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(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

(57) Abstract: Novel benzamide compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful *in vitro*or *in vivo* for preventing or treating coagulation disorders.

BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

Cross Reference to Related Applications

This application claims benefit of priority under 35 U.S.C.§ 119(e) to U.S. Provisional Application No. 60/185,746 filed on February 29, 2000 and U.S. Provisional Application No. 60/154,332 filed on September 17, 1999 filed on September 17, 1999, each of which is herein incorporated in its entirety by reference.

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the

Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25, 4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985);

Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to thrombin are desired, especially those compounds having good bioavailability and/or solubility.

Summary of the Invention

The present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have

particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention relates to a compound according to the formula:

A-Q-D-E-G-J-X

wherein:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are

selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, $-CO_2R^1$, $-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-NO_2$, $-SO_2N(R^1, R^2)$, $-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_mNR^1-$ group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-CF_3$, $-OR^2$, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, $-C_1-C_4$-alkyl, $-C_{1-4}$alkyl-CN, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, $-OR^5$, $-N(-R^5, -R^6)$, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylphenyl and $-C_{0-4}$alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-;

R^7 is selected from:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are

selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

-C_{1-2}-alkyl-, -O-, -S-, -SO-, -SO_2-, -C_{0-1}-alkyl-C(=O), -C_{0-1}-alkyl-C(=O)-N(-R^8)-C_{0-1}-alkyl-, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, -N(-R^8)-C(=O)-N(-R^8)- and -C_{0-1}-alkyl-N(-R^8)-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-C(=O)-OH, -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered

heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; -NO_2; -$(CH_2)_{0-6}$-N$R^{2d}R^{3d}$; -SO_2N$R^{2d}R^{3d}$; -SO_2R^{2d}; -CF_3; -$(CH_2)_{0-6}$-OR^{2d}; -O-$(CH_2)_{1-6}$OR^{2d}; -O-$(CH_2)_{1-6}$-C(=O)-O-R^{2d};
-O-$(CH_2)_{1-6}$-C(=O)-N(R^{2d},R^{3d}); -N(R^{5a})-$(CH_2)_{1-6}$-OR^{2d};
-N(R^{5a})-$(CH_2)_{1-6}$-N(R^{2d},R^{3d}); -C(=O)-N(R^{2d},R^{3d});
-N(R^{5a})-$(CH_2)_{1-6}$-C(=O)-N(R^{2d},R^{3d}); -N(-$(CH_2)_{1-6}$-OR^{2d})$_2$; -N(R^{5a})-$(CH_2)_{1-6}$-OR^{2d};

$-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; a $-(CH_2)_{0-6}-N(R^{3d})C_{5-6}$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:

$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; -O-; -S-; -SO-; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; $-C_{1-4}$-alkyl; carbocyclic aryl; $-C_{0-2}$-alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$-alkyl-C(=O)-O-R^{2e}; $-C_{0-2}$- alkyl-C(=O)-N(R^{2e}, R^{3e}); $-C_{0-2}$-alkyl-NO_2; $-C_{0-2}$-alkyl-N(R^{2e}, R^{3e}); $-C_{0-2}$-alkyl-SO_2-N(R^{2e}, R^{3e}); $-C_{0-2}$-alkyl-SO_2-R^{2e}; trihaloalkyl; $-O-C_{0-2}$-alkyl-O-R^{2e}; $-C_{0-2}$-alkyl-O-R^{2e}; $-O-C_{1-4}$-alkyl-C(=O)-N(R^{2e}, R^{3e}); $-O-C_{1-4}$-alkyl-C(=O)-O-R^{2e}; $-C_{0-2}$-alkyl-N(R^{2e})-C(=O)-R^{3e}; $-C_{0-2}$-alkyl-N(-R^{2e})-SO_2-R^{3e}; $-CH_2$-N(R^{2e})-C(=O)-R^{3e} ;$-CH_2$-N(R^{2e})-SO_2-R^{3e}; $-(CH_2)_{0-6}$-N$R^{2e}R^{3e}$; -C(=O)-N(R^{2e},R^{3e}); -N(-$(CH_2)_{1-6}$-OR^{2e})$_2$; -N(R^{10})-$(CH_2)_{1-6}$-OR^{2e}; -N(R^{10})-C(=O)-R^{2e}; -N(R^{10})-SO_2-R^{2e}; -C(=N(R^{10}))-N(R^{2e},R^{3e}); and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-2}$-alkyl-O-R^{1g}; $-C_{0-2}$-alkyl-N(-R^{1g}, -R^{2g});$-C_{1-4}$-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; $-C_{1-4}$-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g})R^{4g}; -C(=O)-OR^{3g}; -NO_2; $-(CH_2)_p$-N$R^{3g}R^{4g}$; -SO_2N$R^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_p$OR^{3g};

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:
H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if

no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl,

carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen

atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary,

secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

In a preferred embodiment the present invention provides a compound according to the formula:

A-Q-D-E-G-J-X

wherein:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -N(R^1,R^2), N(R^1,R^2)-C(=NR^3)-, N(R^1,R^2)-C(=NR^3)-N(R^4)-, R^1-C(=NR^3)-, R^1-C(=NR^3)-N(R^4)-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, -CO_2R^1, -C(=O)-N(R^1, R^2), -$(CH_2)_m$-CO_2R^1, -$(CH_2)_m$-C(=O)-N(R^1, R^2), -NO_2, -SO_2N(R^1, R^2), -SO_2R^1, -$(CH_2)_m$NR^1R^2, -$(CH_2)_m$-C(=NR^3)-R^1, -$(CH_2)_m$-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$-N(R^4)-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$NR^1- C_{3-6}heterocyclics, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, -CF_3, -OR^2, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, CN-C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, -OR^5, -N(-R^5, -R^6), -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from

1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-;

R^7 is selected from:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:
-C_{1-2}-alkyl-, -O-, -S-, -SO-, -SO_2-, -C_{0-1}-alkyl-C(=O), -C_{0-1}-alkyl-C(=O)-N(-R^8)-C_{0-1}-alkyl-, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, -N(-R^8)-C(=O)-N(-R^8)- and -C_{0-1}-alkyl-N(-R^8)-;

R^8 is a member selected from the group consisting of:
H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-C(=O)-OH, -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:
H, -C_{1-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:
Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:
H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein C_2-alkenyl or C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}--N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; and $-(CH_2)_{0-6}-N(-R^{3d})-$ group attached directly by its nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}-$ group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:
$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:
H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:
Halo; CF_3; $-C_{1-4}$-alkyl; carbocyclic aryl; $-C_{0-2}$-alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$- alkyl-$C(=O)-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-NO_2; $-C_{0-2}$-alkyl-$N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-$SO_2-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-SO_2-R^{2e}; trihaloalkyl; $-O-C_{0-2}$-alkyl-$O-R^{2e}$; $-C_{0-2}$-alkyl-$O-R^{2e}$; $-O-C_{1-4}$-alkyl-

$C(=O)$-$N(R^{2e}, R^{3e})$; -O-C_{1-4}-alkyl-$C(=O)$-O-R^{2e}; -C_{0-2}-alkyl-$N(R^{2e})$-$C(=O)$-R^{3e}; -C_{0-2}-alkyl-$N(-R^{2e})$-SO_2-R^{3e}; -CH_2-$N(R^{2e})$-$C(=O)$-R^{3e} ;-CH_2-$N(R^{2e})$-SO_2-R^{3e}; -$(CH_2)_{0-6}$-$NR^{2e}R^{3e}$; -$C(=O)$-$N(R^{2e},R^{3e})$; -$N(-(CH_2)_{1-6}$-$OR^{2e})_2$; -$N(R^{10})$-$(CH_2)_{1-6}$-OR^{2e}; -$N(R^{10})$-$C(=O)$-R^{2e}; -$N(R^{10})$-SO_2-R^{2e}; -$C(=N(R^{10}))$-$N(R^{2e},R^{3e})$; and a -$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-$N(-R^{1g}$, -$R^{2g})$;-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -$C(=O)$-$N(R^{3g})R^{4g}$; -$C(=O)$-OR^{3g}; -NO_2; -$(CH_2)_p$-$NR^{3g}R^{4g}$; -$SO_2NR^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a further preferred embodiment the present invention provides a compound according to the formula:

A-Q-D-E-G-J-X

wherein:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -N(R^1,R^2), N(R^1,R^2)-C(=NR^3)-, N(R^1,R^2)-C(=NR^3)-N(R^4)-, R^1-C(=NR^3)-, R^1-C(=NR^3)-N(R^4)-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, -CO_2R^1, -C(=O)-N(R^1, R^2), -$(CH_2)_m$-CO_2R^1, -$(CH_2)_m$-C(=O)-N(R^1, R^2), -NO_2, -SO_2N(R^1, R^2), -SO_2R^1, -$(CH_2)_m$NR^1R^2, -$(CH_2)_m$-C(=NR^3)-R^1, -$(CH_2)_m$-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$-N(R^4)-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$NR^1- group attached to a 3-6 membered heterocylic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CF_3, -OR^2, and a 5-6 membered heterocylic aromatic or partially saturated system, including imidazoline, containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocylic system may be independently replaced with a member selected from the group consisting of halo, -methyl, -C_2-C_4-alkyl, -CN, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, -OR^5, -N(-R^5, -R^6), -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties

may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -NH-, -NMe-, -$NHCH_2$-, -$NMeCH_2$-, -CH_2NH-, -C(=NH)-, -C(=O)-NH-, -NH-C(=O)-, -CH_2NMe-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, $-NO_2$, $-(CH_2)_nNR^{2a}R^{3a}$, $-(CH_2)_nCO_2R^{2a}$, $-(CH_2)_nCONR^{2a}R^{3a}$, $-SO_2NR^{2a}R^{3a}$, $-SO_2R^{2a}$, $-CF_3$, $-OR^{2a}$, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylphenyl and $-C_{0-4}$alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN and $-NO_2$;

n is an integer of 0-2;

E is a member selected from the group consisting of:

a direct link, -O-, -NH-, $-CH_2NH-$, $-NHCH_2-$, -NMe-, -NH-C(=O)-NH-, -C(=O)-NH-, -NH-C(=O)-;

G is a member selected from the group consisting of:

(a) a C_2-alkenyl group or a C_{3-8}-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon

atoms and wherein the C_2-alkenyl group or C_{3-8}-cycloalkenyl group is substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$;
$-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$;
$-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$;
$-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$;
$-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$;
$-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; and a $-(CH_2)_{0-6}-N(R^{3d})$ group wich is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}-$ group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a member selected from the group consisting of:

a direct link, -O-, -NH-, -NMe-, -C(=O)-NH-, -NH-C(=O)-;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; $-C_{1-4}$-alkyl; carbocyclic aryl; $-C_{0-2}$-alkyl-CN; $-O-R^{2e}$; $-C_{0-2}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$- alkyl-$C(=O)-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-NO_2; $-C_{0-2}$-alkyl-$N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-$SO_2-N(R^{2e}, R^{3e})$; $-C_{0-2}$-alkyl-SO_2-R^{2e}; trihaloalkyl; $-O-C_{0-2}$-alkyl-$O-R^{2e}$; $-C_{0-2}$-alkyl-$O-R^{2e}$; $-O-C_{1-4}$-alkyl-$C(=O)-N(R^{2e}, R^{3e})$; $-O-C_{1-4}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$-alkyl-$N(R^{2e})-C(=O)-R^{3e}$; $-C_{0-2}$-alkyl-$N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(R^{2e})-C(=O)-R^{3e}$;$-CH_2-N(R^{2e})-SO_2-R^{3e}$; $-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e},R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e},R^{3e})$; and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-N(-R^{1g}, -R^{2g});-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g},R^{4g}); -C(=O)-OR^{3g}; -NO_2; -$(CH_2)_p$-N$R^{3g}R^{4g}$; -SO_2N$R^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_p$OR^{3g};

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

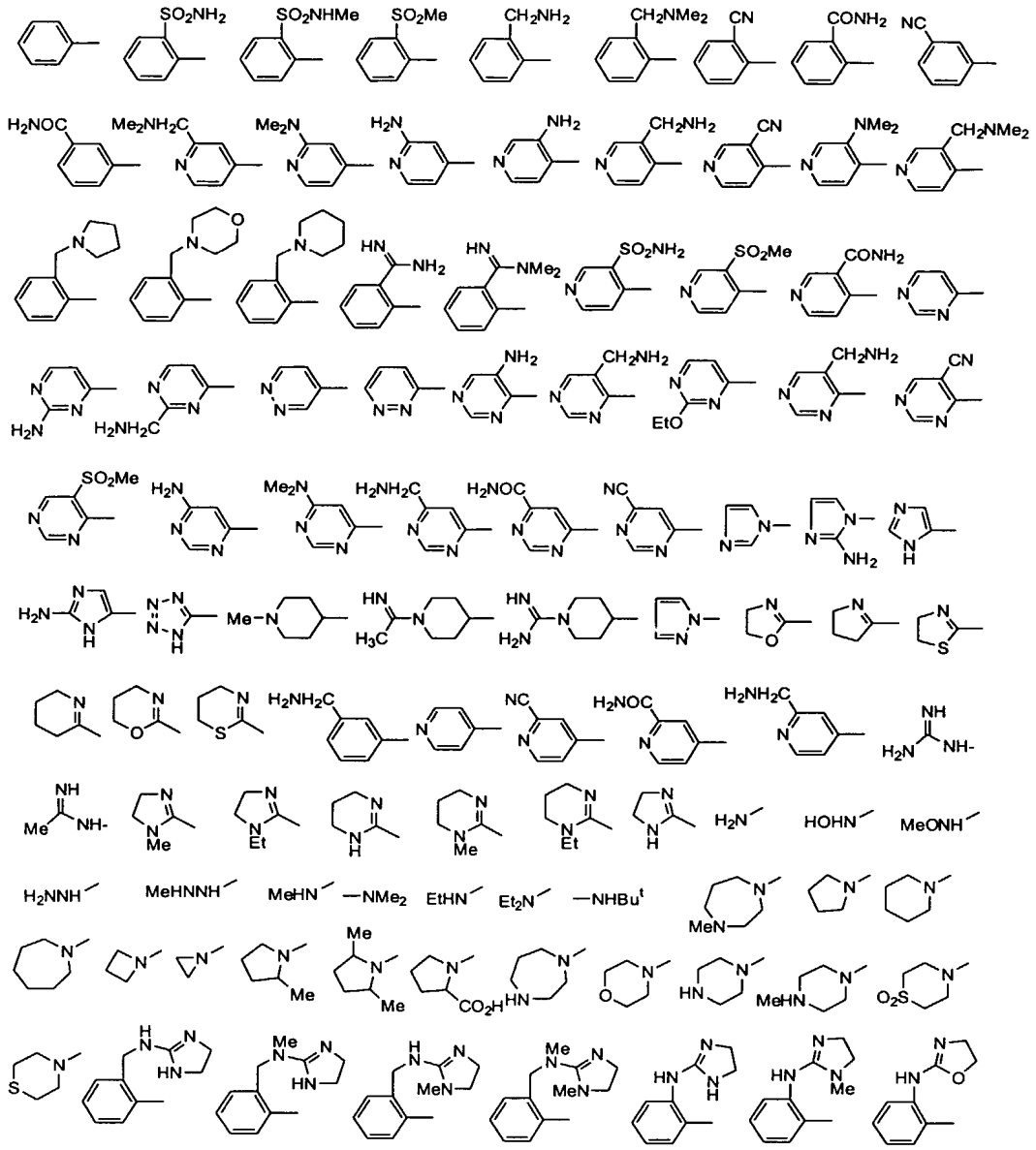
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In a still further preferred embodiment the present invention provides a compound according to the formula:

A-Q-D-E-G-J-X

wherein:

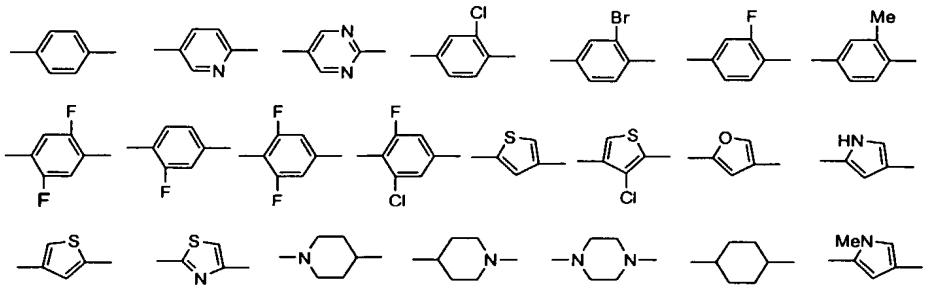
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link, -C(=O)-, -NH-, -NMe-, -NHCH$_2$-, -NMeCH$_2$-, -C(=NH)-, -C(=NMe)-;

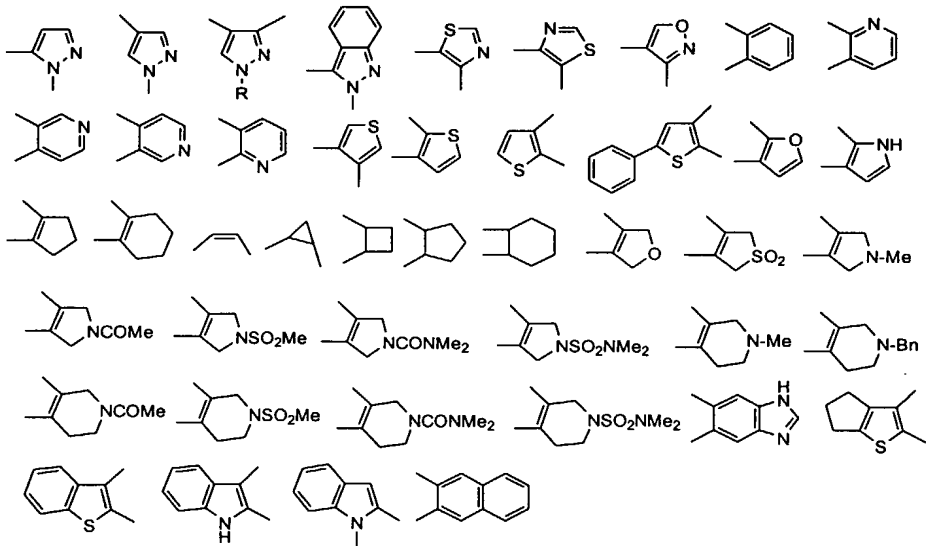
D is a direct link or is a member selected from the group consisting of:



E is a member selected from the group consisting of:

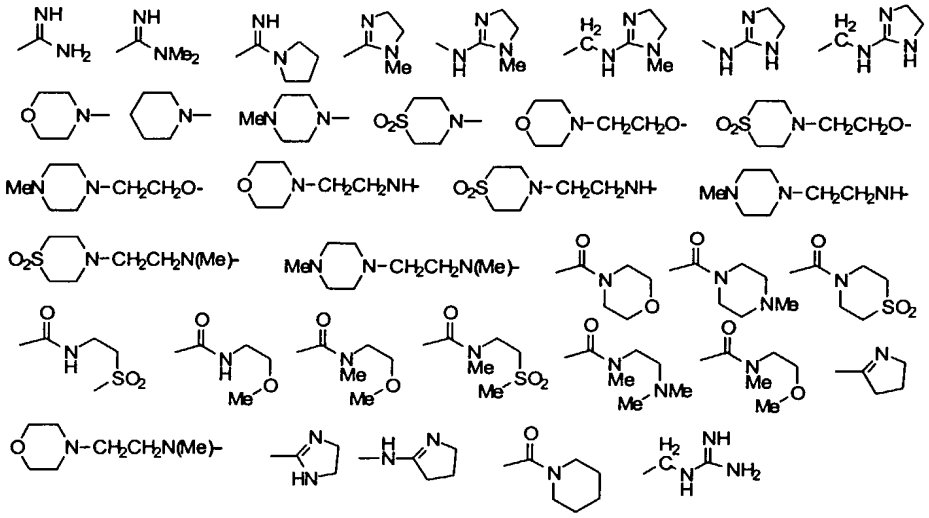
a direct link, $-CH_2NH-$, $-C(=O)-NH-$, $-NH-C(=O)-$;

G is a member selected from the group consisting of:



G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

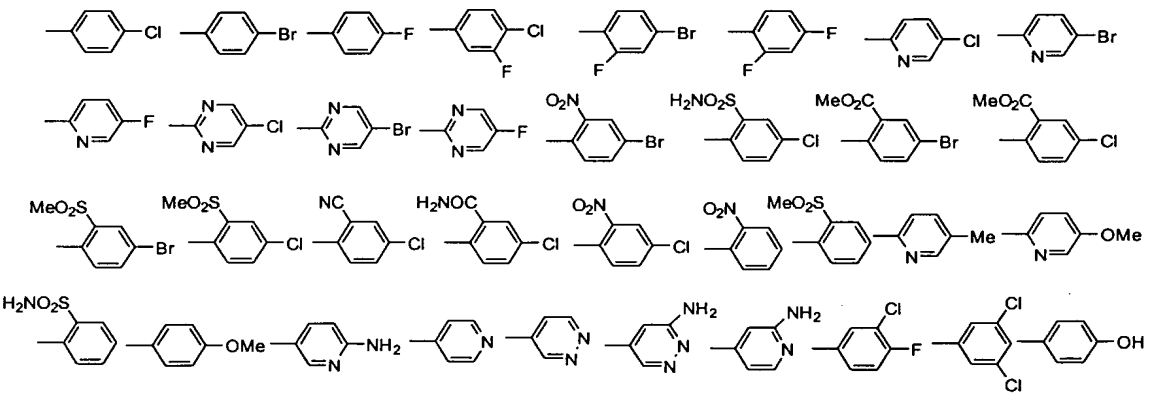
H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-NMe_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, $-C(=O)-OMe$, $-CO_2H$, $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHC(=O)Me$, $-C(=O)N(-Me)_2$, $-CH_2NH_2$, $-CH_2N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$ and $-OCH_2C(=O)N(-Me)_2$.

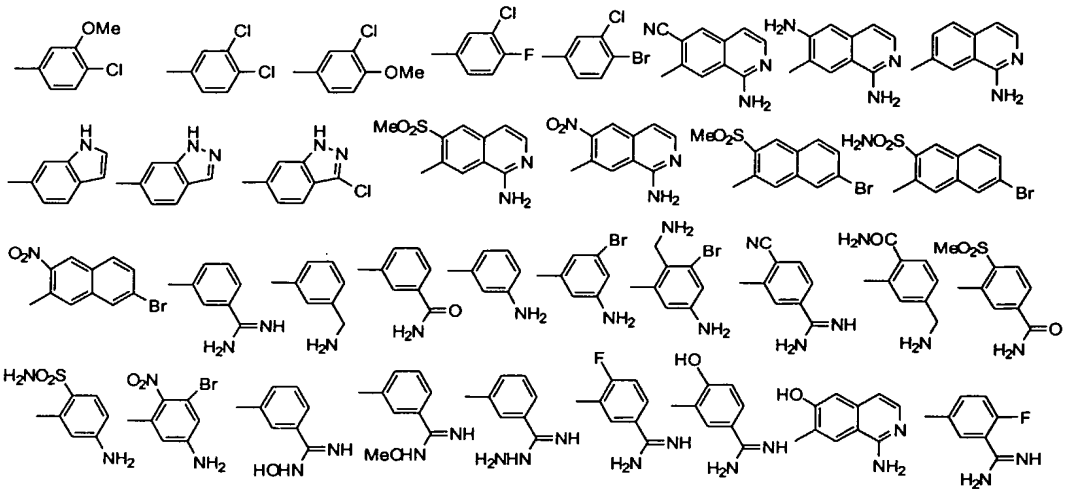


J is a member selected from the group consisting of:

a direct link, -O-, -NH-, -C(=O)-NH- and -NH-C(=O)-;

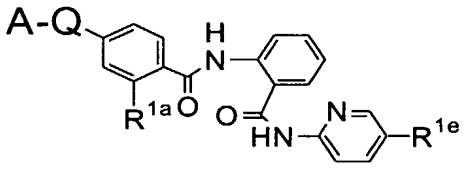
X is a member selected from the group consisting of:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

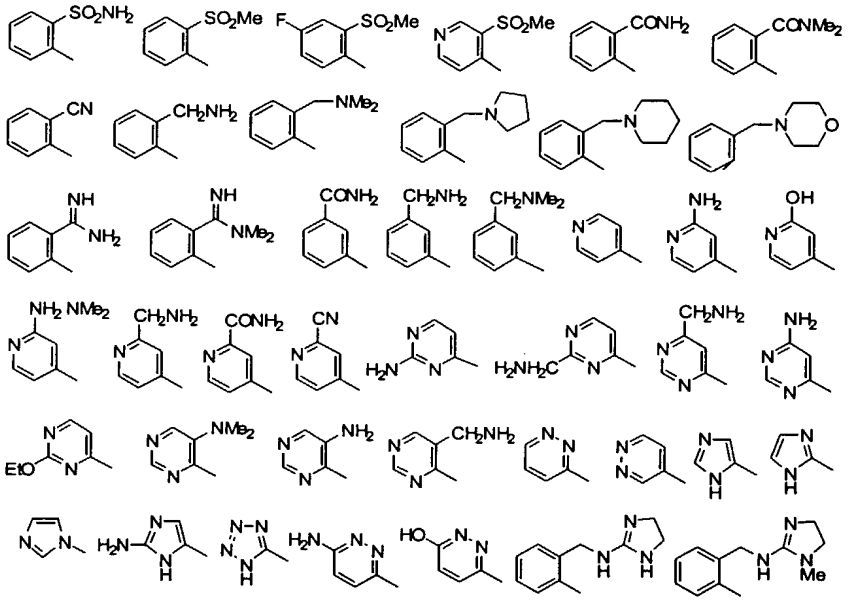
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

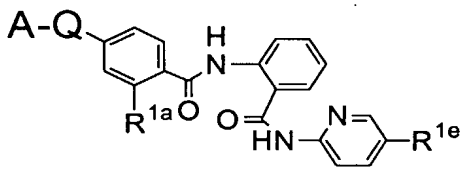
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

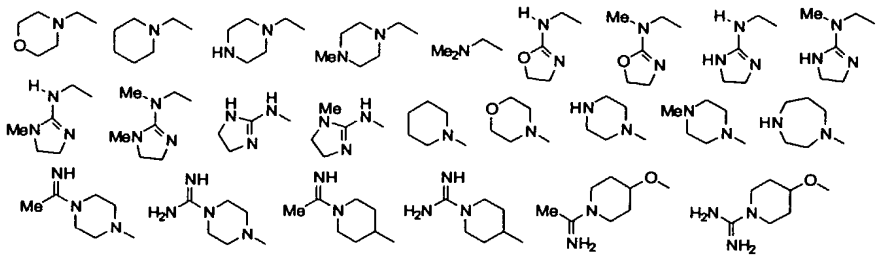
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

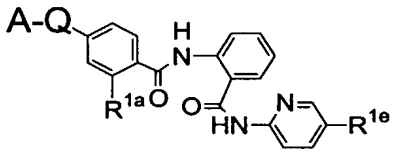
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

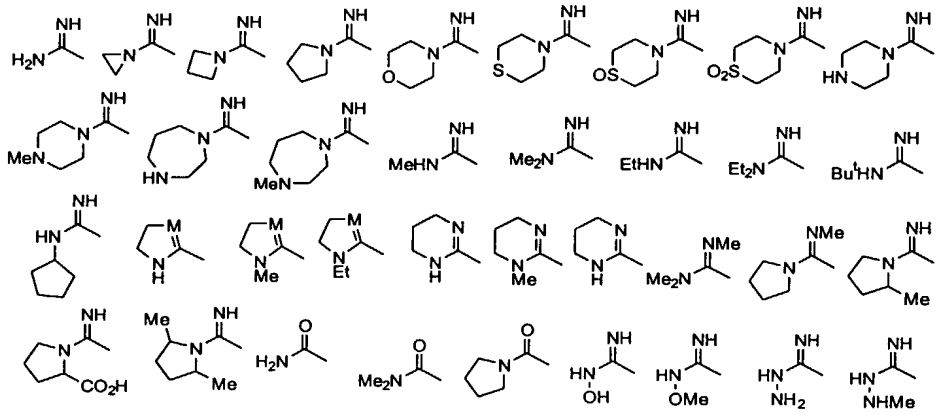
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

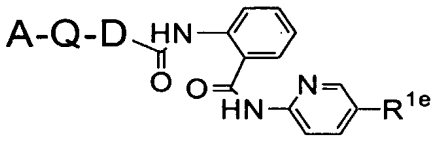
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:

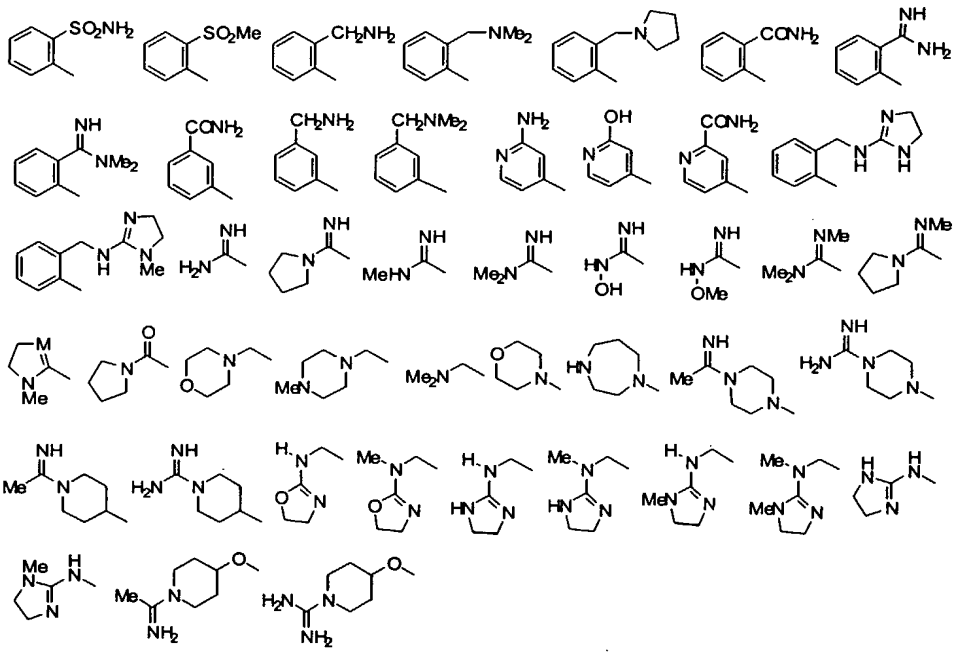


wherein:

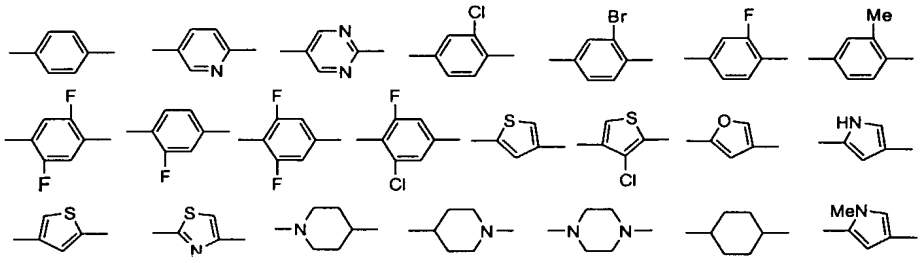
R^{1e} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$;

A-Q is a member selected from the group consisting of:

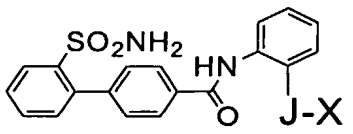


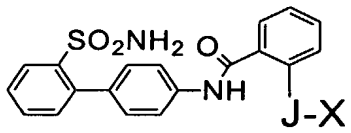
D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound according to the formula:



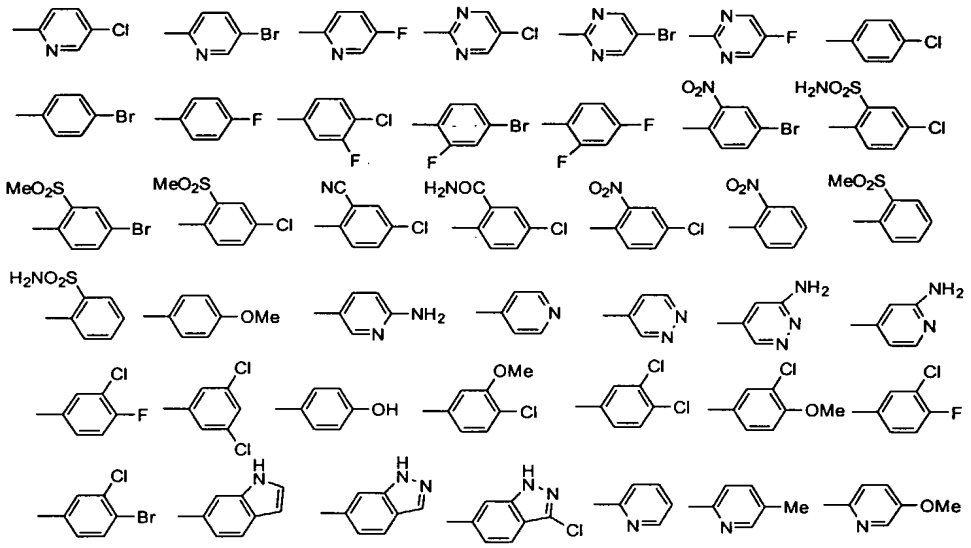


wherein:

J is a member selected from the group consisting of:

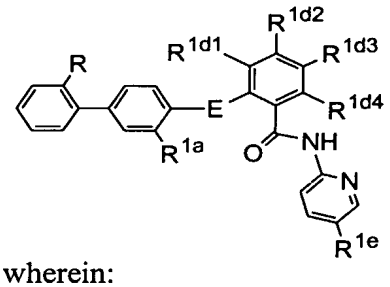
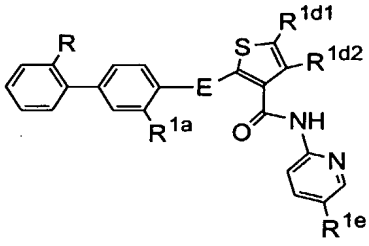
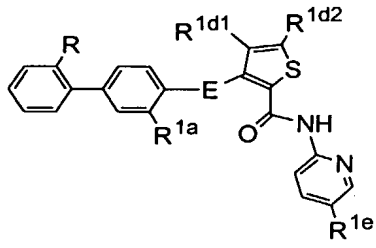
-NHC(=O)-, -C(=O)NH-;

X is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment the present invention provides a compound according to the formula:

wherein:

R is a member selected from the group of :

$-SO_2-NH_2$ and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

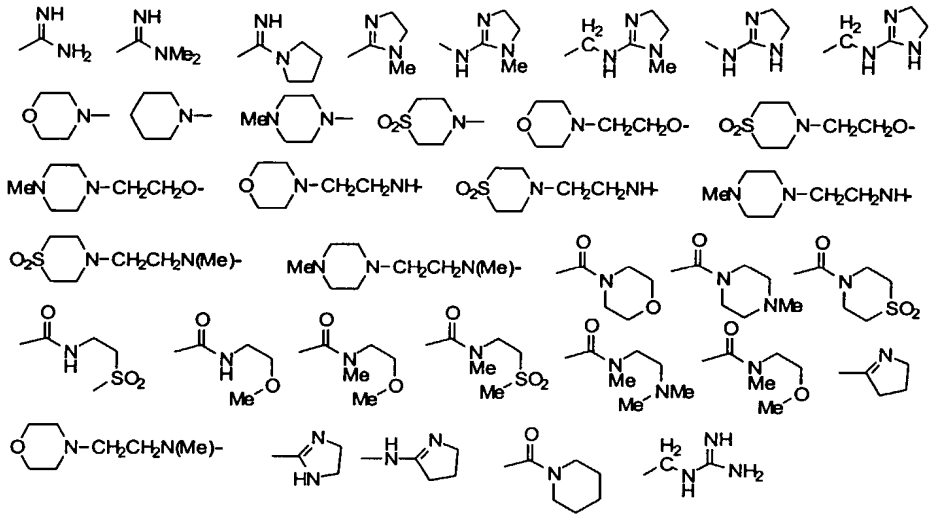
-NHC(=O)- and -C(=O)NH-;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$ and $-CH_2NH_2$;

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me, $-C(=O)-N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$, and $-OCH_2C(=O)-N(-Me)_2$,

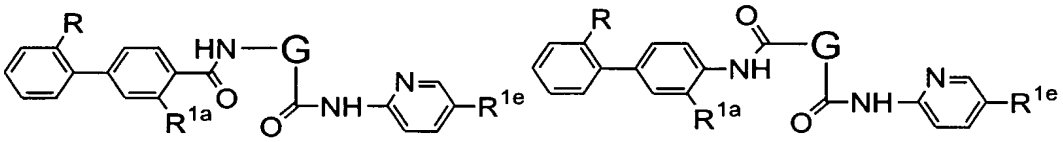


R^{1e} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and –Ome,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

R is a member selected from the group consisting of:

$-SO_2NH_2$, $-SO_2Me$;

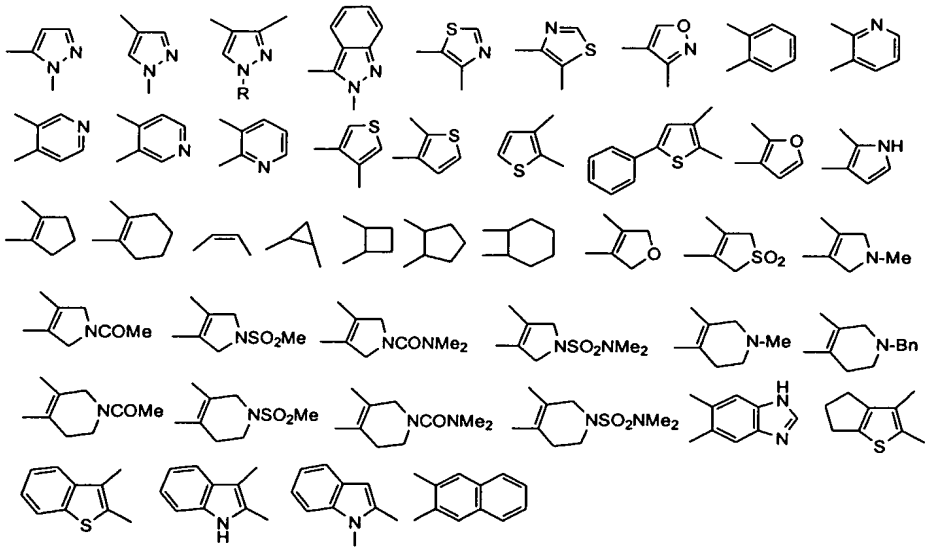
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

R^{1e} is a member selected from the group consisting of:

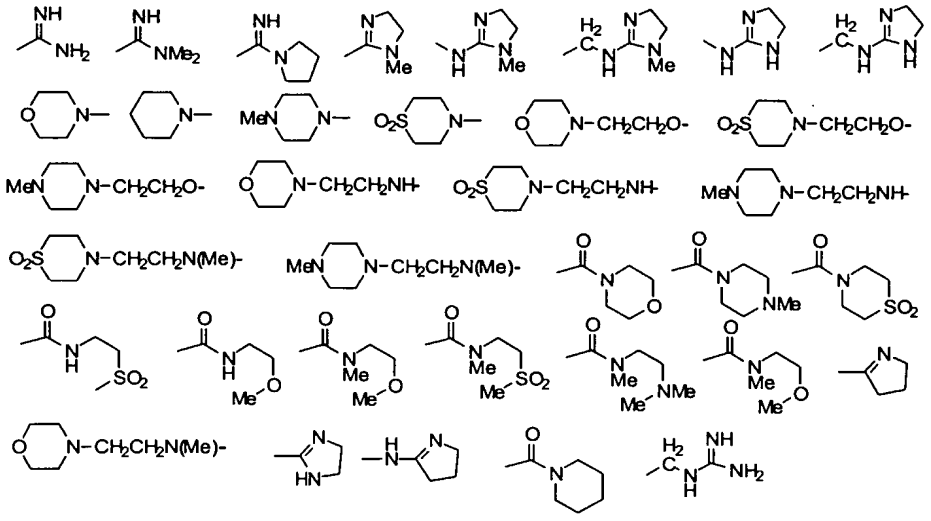
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

G is a member selected from the group consisting of:



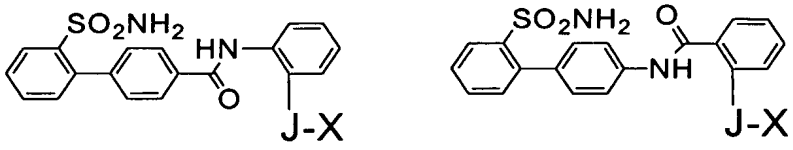
wherein each G group may be substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, -C(=O)-NH_2, $-SO_2NH_2$, $-SO_2CH_3$, -NH-C(=O)-Me, -C(=O)-$N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2C(=O)-NH_2$, $-OCH_2C(=O)-N(-Me)_2$



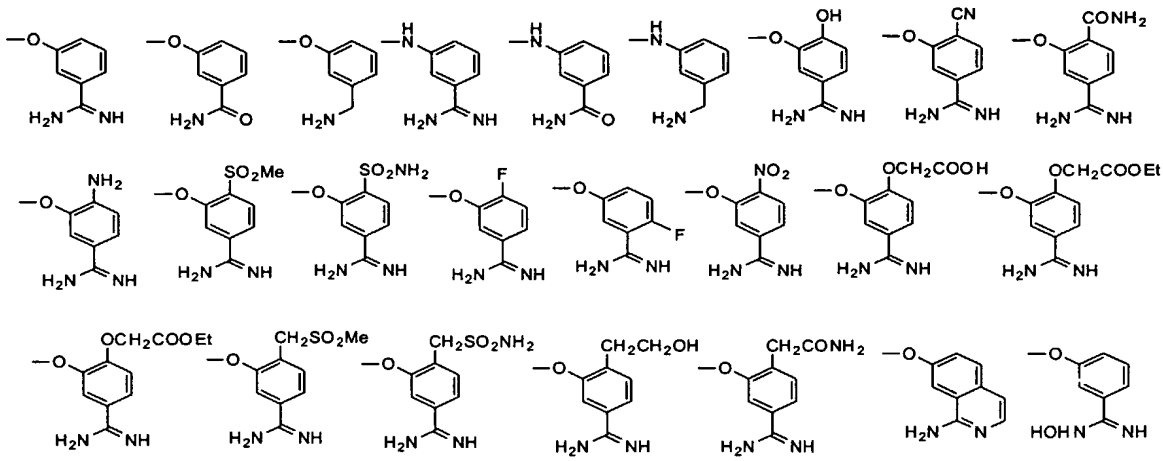
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



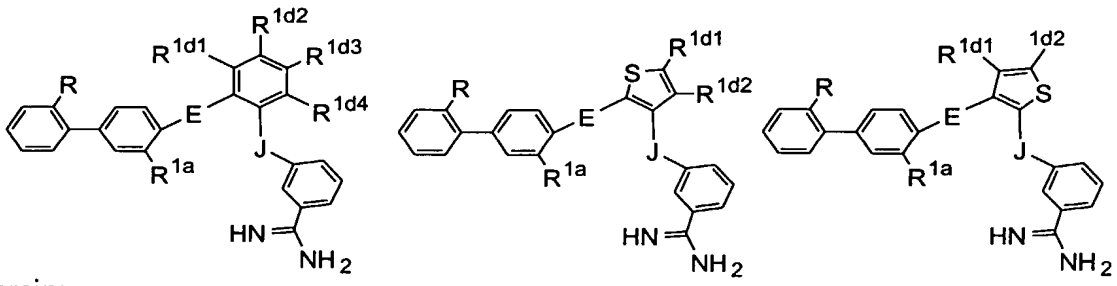
wherein:

J-X are collectively a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound
according to the formula:



wherein:

R is a member selected from the group of :

$-SO_2NH_2$, and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

-NHC(=O)- and -C(=O)NH-;

J is a member selected from the group consisting of:

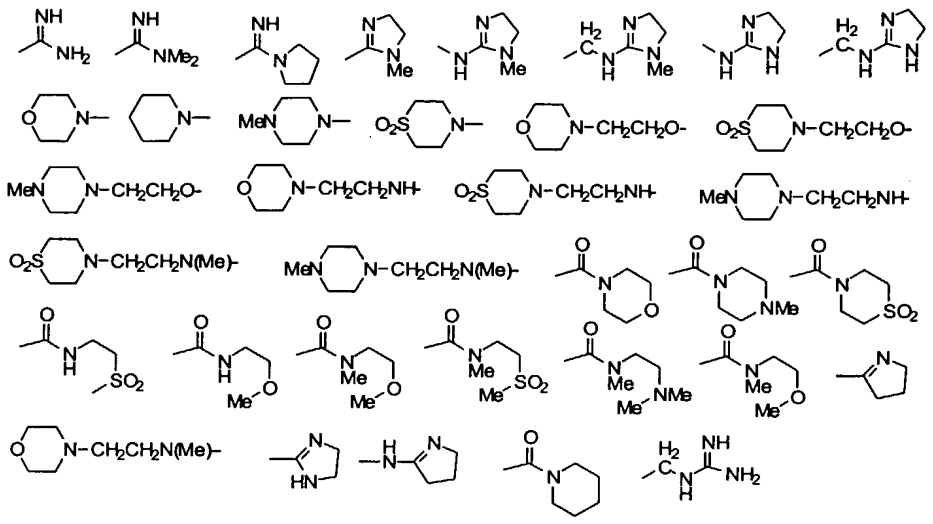
-NHC(=O)- and -C(=O)NH-, O;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$, $-CH_2NH_2$;

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, $-CO_2Me$, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me, $-C(=O)-N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$, $-OCH_2C(=O)-N(-Me)_2$,

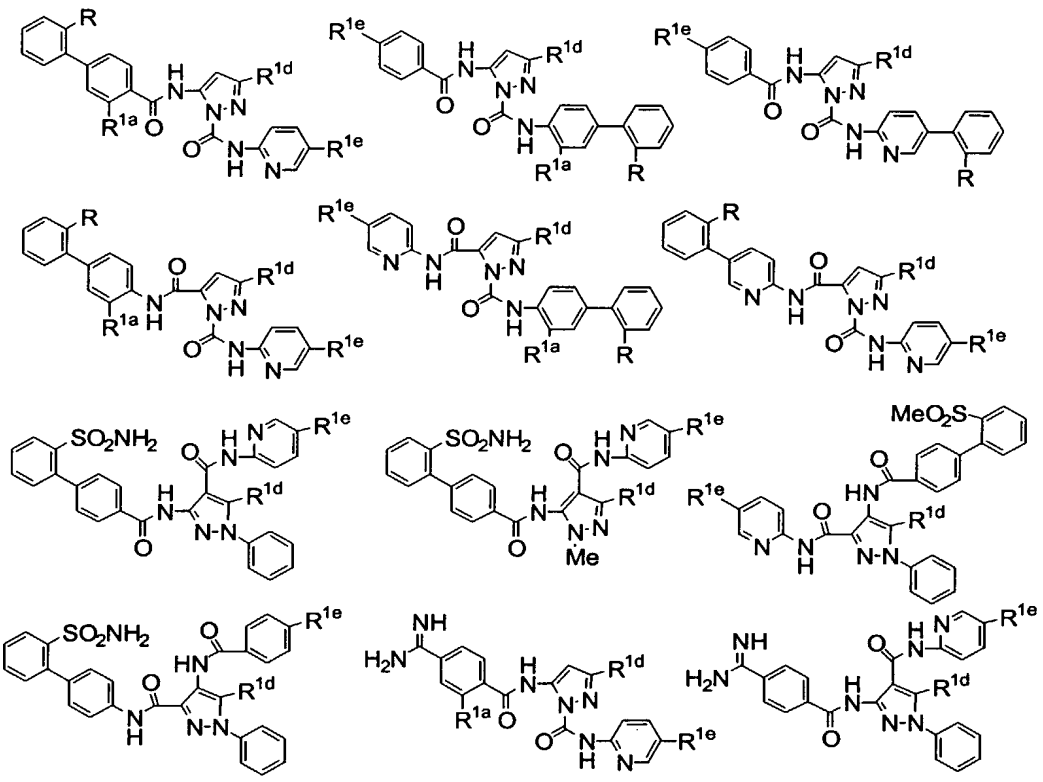


R^{1e} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and -OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for G, particularly when G is a pyrazole ring structure.



wherein:

R is a member selected from the group of :

$-SO_2-NH_2$, and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

R^{1d} is a member selected from the group consisting of:

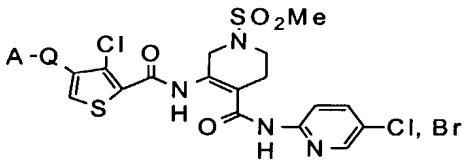
$-H$, $-CH_3$, $-CF_3$, $-CN$, $-SO_2NH_2$ and $-SO_2CH_3$; and

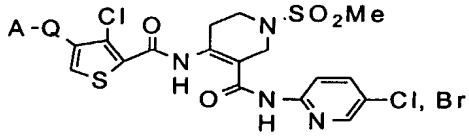
R^{1e} is a member selected from the group of:

-Cl and -Br;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

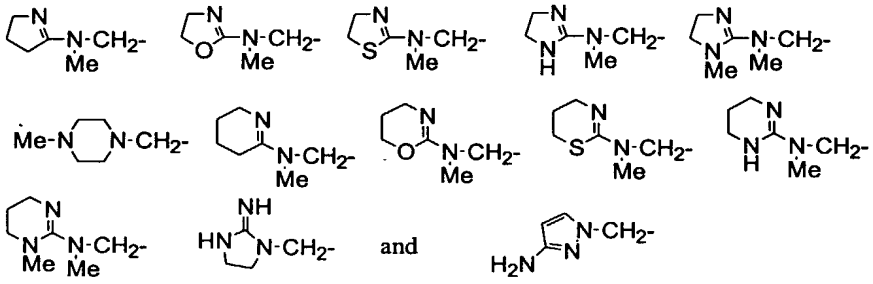
In another preferred embodiment the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for A-Q taken collectively when the remainder of the compound structure has the one of the following two formulae:





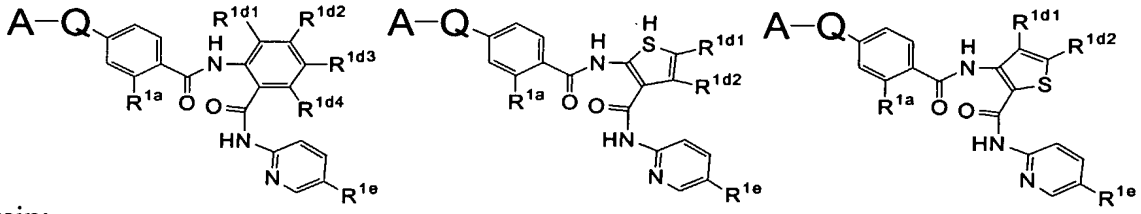
wherein:

A-Q taken together are a member selected from the group consisting of:



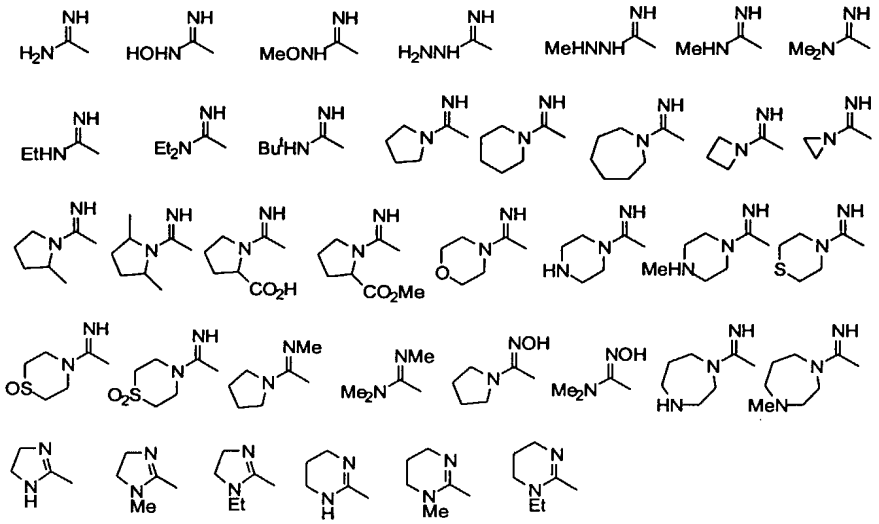
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound according to the formula:



wherein:

A-Q is a member selected from the group of :



R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

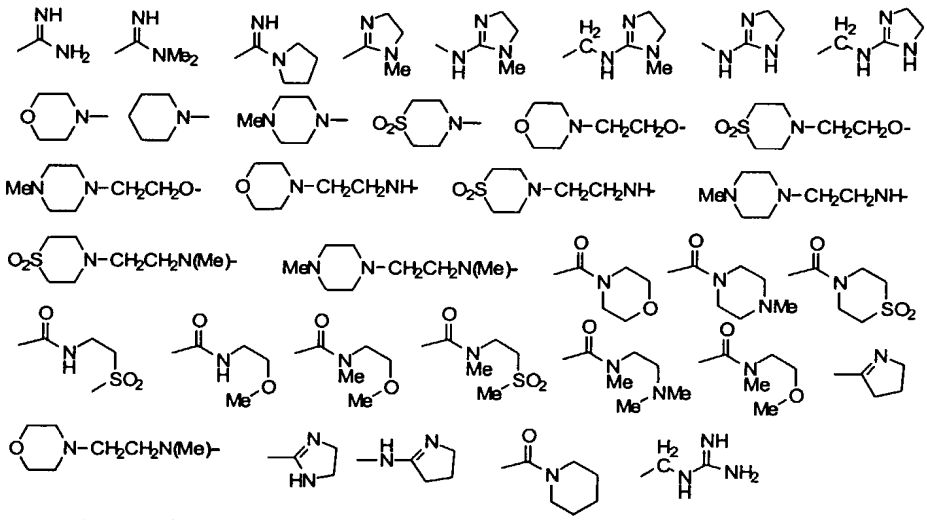
R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$, $-CH_2NH_2$

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me,

-C(=O)-N(Me)$_2$, -CH_2NH_2, -CH_2-N(-Me)$_2$, -CH_2OH, -OCH_2CO_2H,
-$OCH_2C(=O)$-OMe, -$OCH_2C(=O)$-NH_2, -$OCH_2C(=O)$-N(-Me)$_2$,

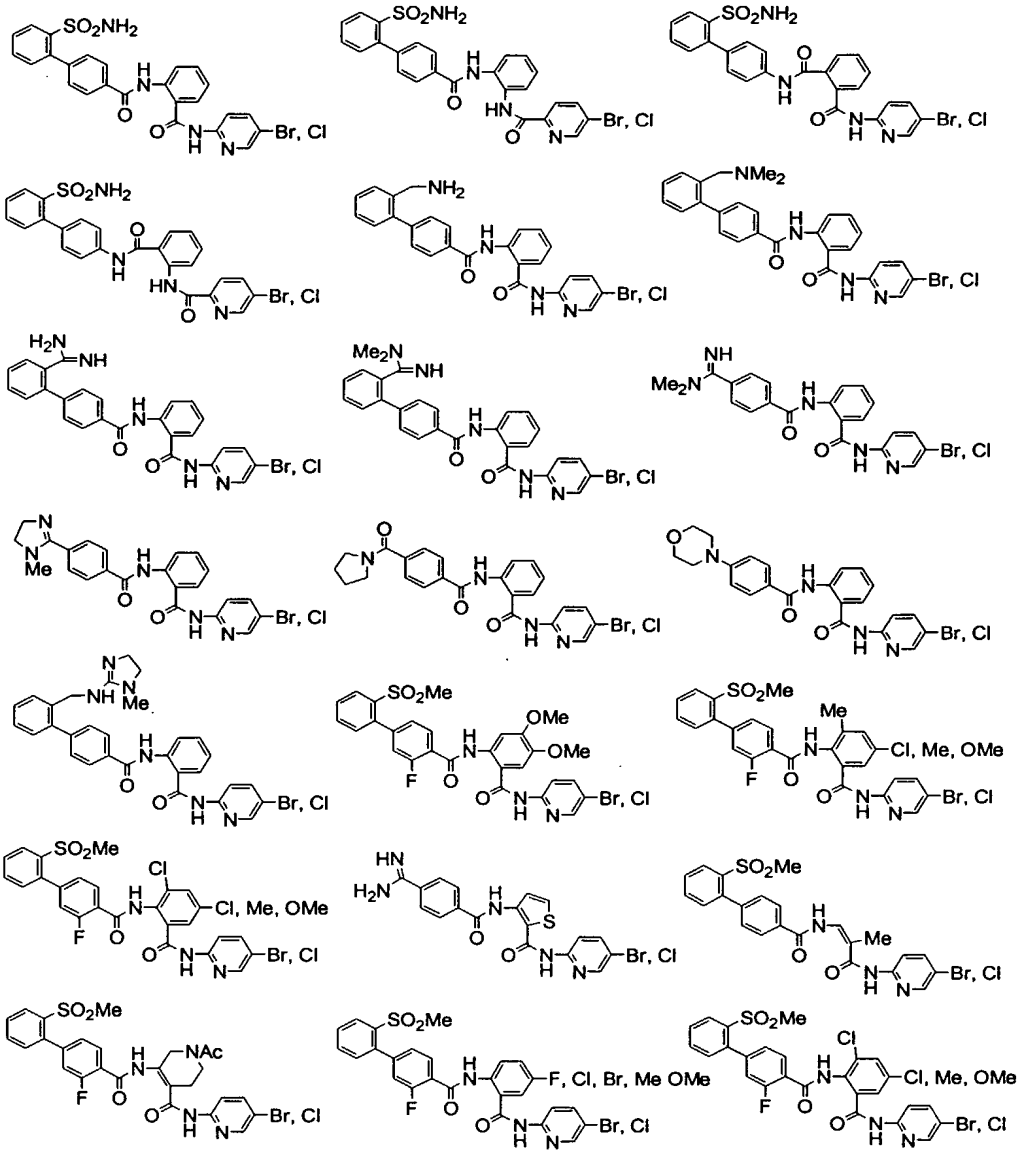


R^{1e} is a member selected from the group of:

F, -Cl, -Br, -OH, -Me and -OMe;

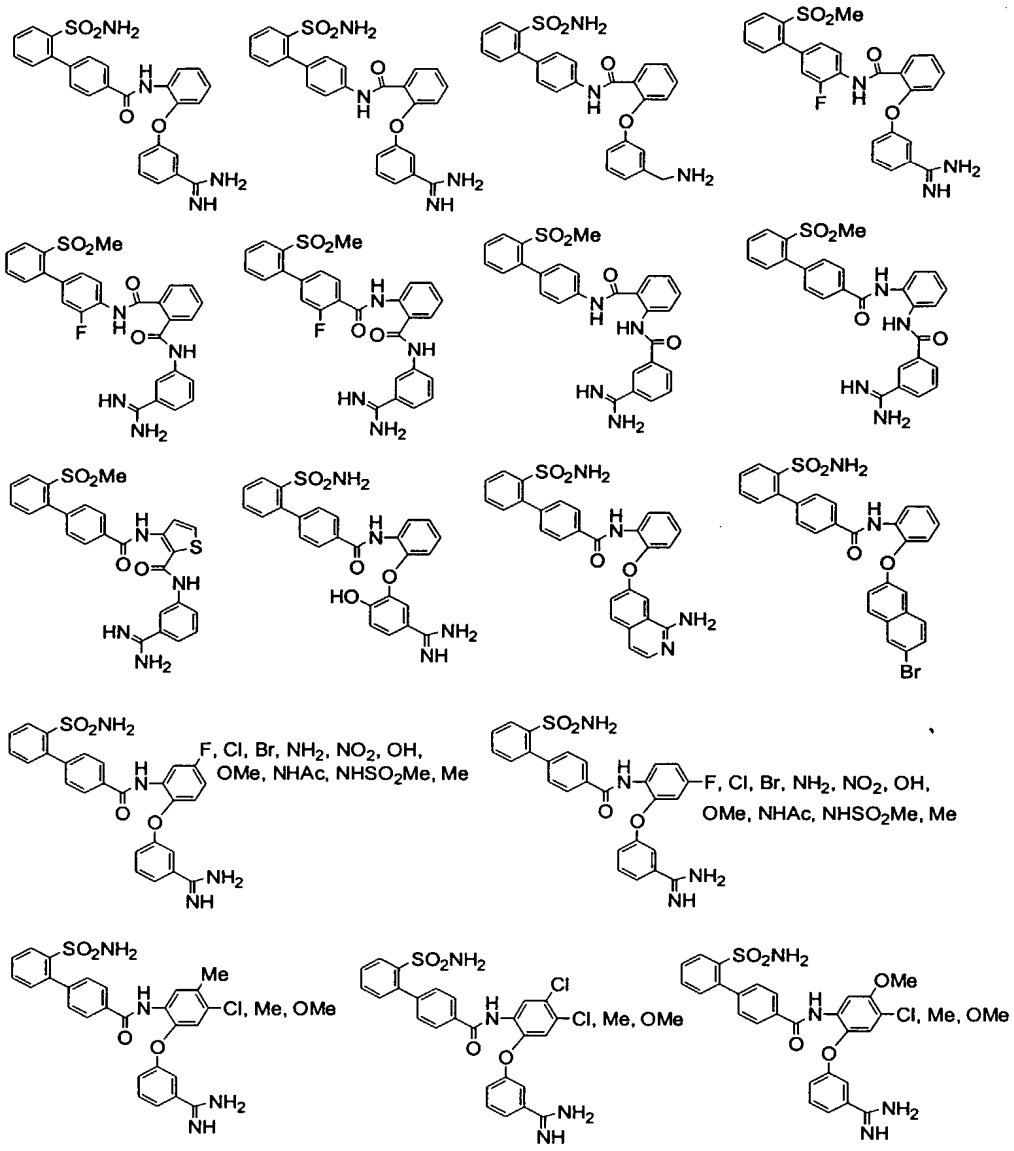
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides the following compounds:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides the following compounds:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates, solvates, and prodrug derivatives of the preferred compounds. In addition, the preferred compounds can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates, solvates, and prodrug derivatives of such isomers and tautomers.

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Prodrug Derivatives of Compounds

This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type

form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature

leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and

be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The

compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other

routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Compounds according to the invention can be synthesized utilizing procedures well known in the art. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography or other appropriate methods.

Compositions and Formulations

The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, reaction of the free acid or free base form of a compound of the structures recited above with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

Diagnostic applications of the compounds of this invention will typically utilize formulations such as solution or suspension. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in *Remington's Pharmaceutical Sciences*, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinalpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose

or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of this invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the factor Xa inhibitors of this invention may be coupled to a class of biodegradable polymers useful in achieving

controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will naturally be influenced by the route of administration, the therapeutic objectives, and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each inhibitor by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be within the ambit of one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

A typical dosage might range from about 0.001 mg/kg to about 1000 mg/kg, preferably from about 0.01 mg/kg to about 100 mg/kg, and more preferably from about 0.10 mg/kg to about 20 mg/kg. Advantageously, the compounds of this invention may be administered several times daily, and other dosage regimens may also be useful.

Typically, about 0.5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder,

preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice. The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin, and excipient such as microcrystalline cellulose, a disintegrating agent like corn starch or alginic acid, a lubricant such as magnesium stearate, a sweetening agent such as sucrose or lactose, or a flavoring agent. When a dosage form is a capsule, in addition to the above materials it may also contain a liquid carrier such as water, saline, a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

In practicing the methods of this invention, the compounds of this invention may be used alone or in combination, or in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this inventions may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice, such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of this invention can be utilized in vivo, ordinarily in mammals such as primates, such as humans, sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The preferred compounds of the present invention are characterized by their ability to inhibit thrombus formation with acceptable effects on classical measures of coagulation parameters, platelets and platelet function, and acceptable levels of bleeding complications associated with their use. Conditions characterized by undesired thrombosis would include those involving the arterial and venous vasculature.

With respect to the coronary arterial vasculature, abnormal thrombus formation characterizes the rupture of an established atherosclerotic plaque which is the major cause of acute myocardial infarction and unstable angina, as well as also characterizing the occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PTCA).

With respect to the venous vasculature, abnormal thrombus formation characterizes the condition observed in patients undergoing major surgery in the lower extremities or the abdominal area who often suffer from thrombus formation in the venous vasculature resulting in reduced blood flow to the affected extremity and a predisposition to pulmonary embolism. Abnormal thrombus formation further characterizes disseminated intravascular coagulopathy commonly occurs within both vascular systems during septic shock, certain viral infections and cancer, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure.

The compounds of this present invention, selected and used as disclosed herein, are believed to be useful for preventing or treating a condition characterized by undesired thrombosis, such as (a) the treatment or prevention of any thrombotically mediated acute coronary syndrome including myocardial infarction, unstable angina, refractory angina, occlusive coronary thrombus occurring post-thrombolytic therapy or post-coronary angioplasty, (b) the treatment or prevention of any thrombotically mediated cerebrovascular syndrome including embolic stroke, thrombotic stroke or transient ischemic attacks, (c) the treatment or prevention of any thrombotic syndrome occurring in the venous system including deep venous thrombosis or pulmonary embolus occurring either spontaneously or in the setting of malignancy, surgery or trauma, (d) the treatment or prevention of any coagulopathy including disseminated intravascular coagulation (including the setting of septic shock or other infection, surgery, pregnancy, trauma or malignancy and whether associated with multi-organ failure or not), thrombotic thrombocytopenic purpura, thromboangiitis obliterans, or thrombotic disease associated with heparin induced thrombocytopenia, (e) the treatment or prevention of thrombotic complications associated with extracorporeal circulation (e.g. renal dialysis, cardiopulmonary bypass or other oxygenation

procedure, plasmapheresis), (f) the treatment or prevention of thrombotic complications associated with instrumentation (e.g. cardiac or other intravascular catheterization, intra-aortic balloon pump, coronary stent or cardiac valve), and (g) those involved with the fitting of prosthetic devices.

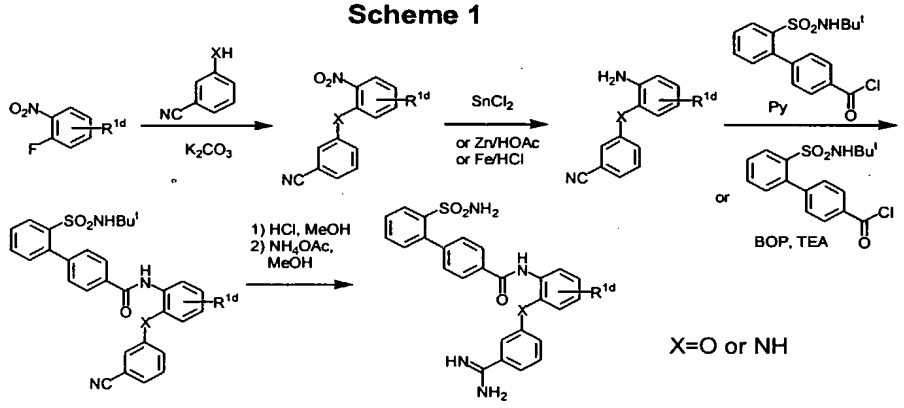
Anticoagulant therapy is also useful to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus the compounds of this invention can be added to or contacted with any medium containing or suspected to contain factor Xa and in which it is desired that blood coagulation be inhibited, e.g., when contacting the mammal's blood with material such as vascular grafts, stents, orthopedic prostheses, cardiac stents, valves and prostheses, extra corporeal circulation systems and the like.

Without further description, it is believed that one of ordinary skill in the art can, using the preceding description and the following illustrative examples, make and utilize the compounds of the present invention and practice the claimed methods.

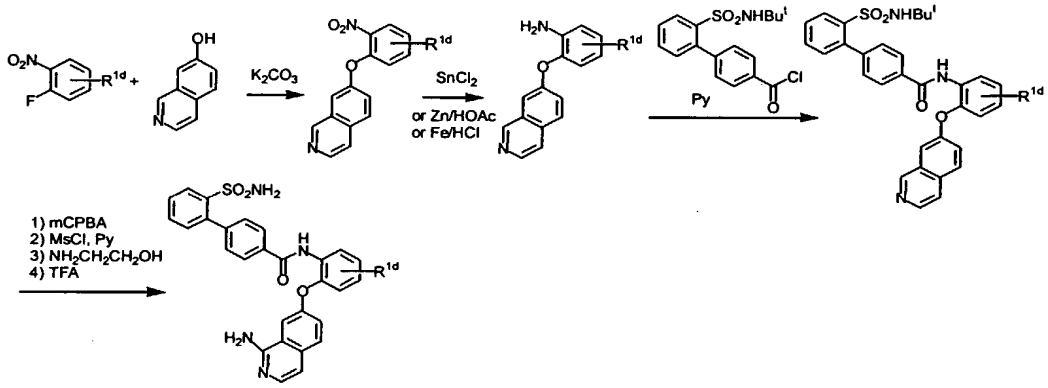
EXAMPLES

Examples of Chemical Production Process General Reaction Schemes

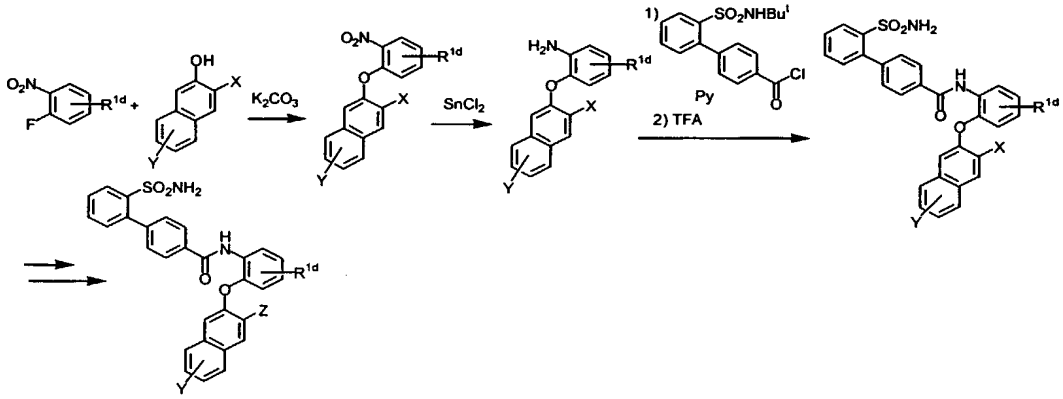
Scheme 1



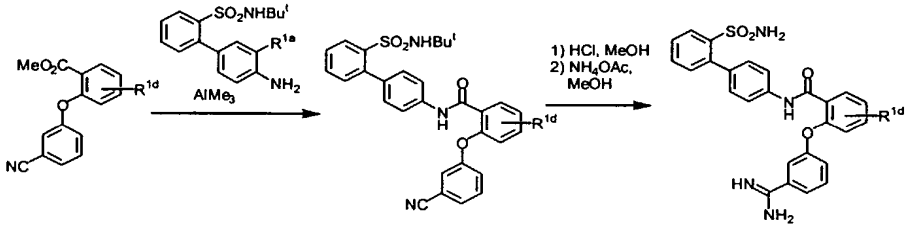
Scheme 2



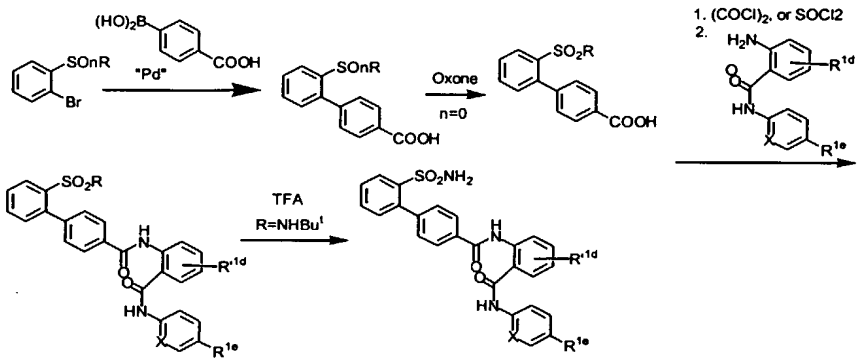
Scheme 3



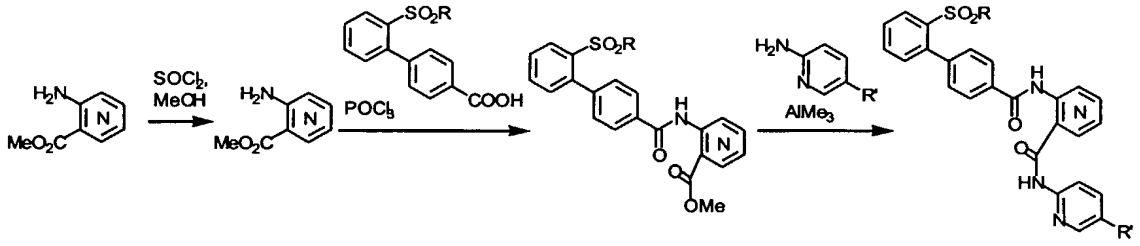
Scheme 4



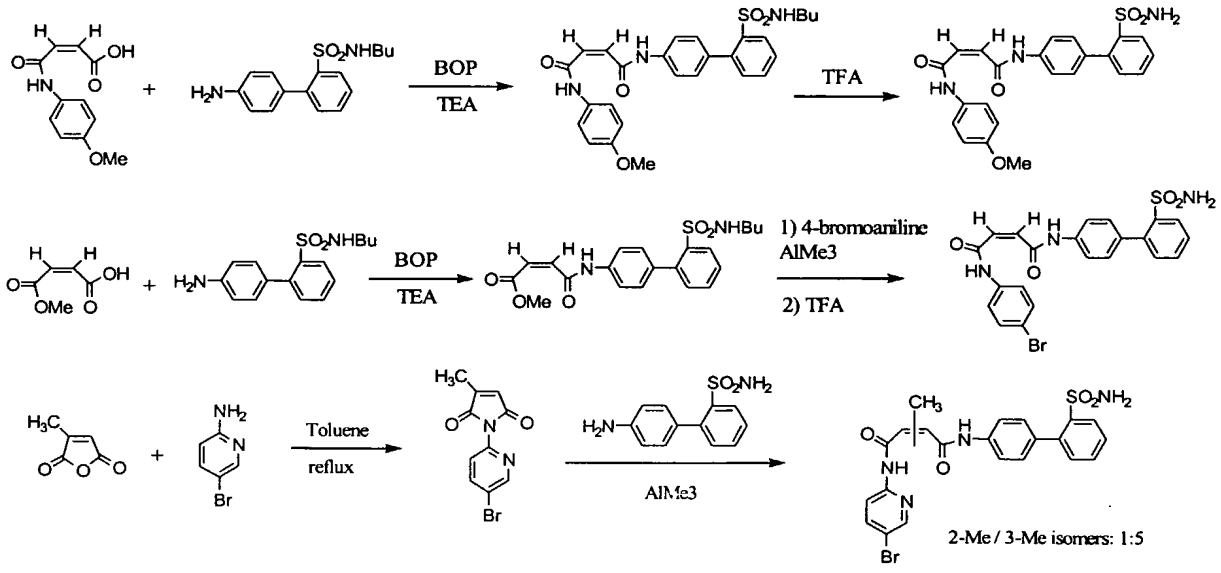
Scheme 5



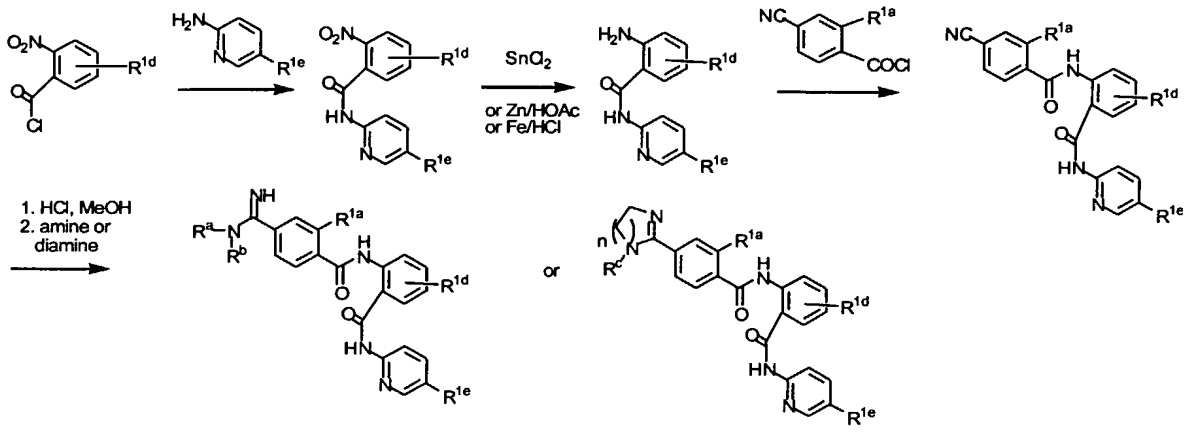
Scheme 6



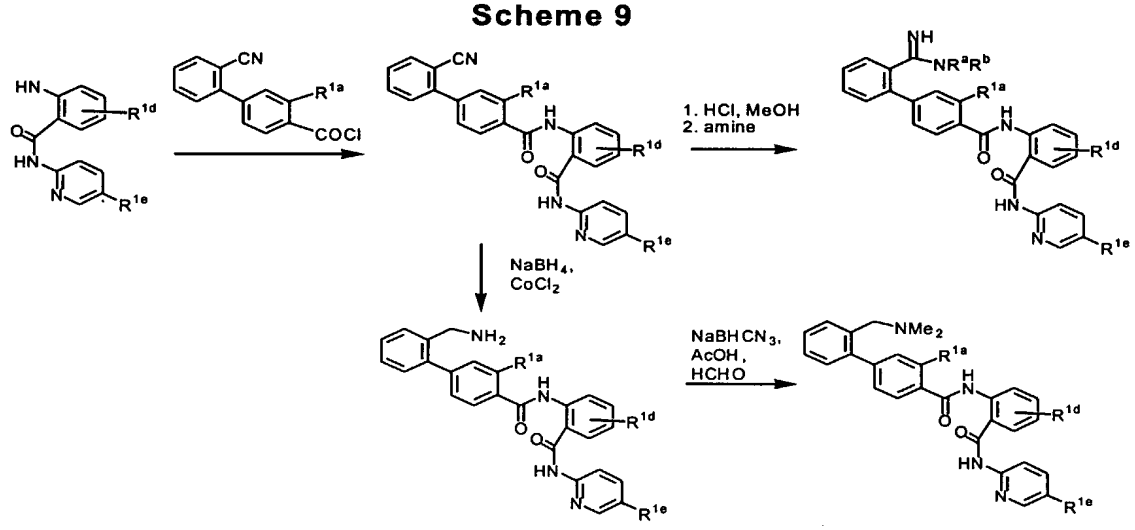
Scheme 7



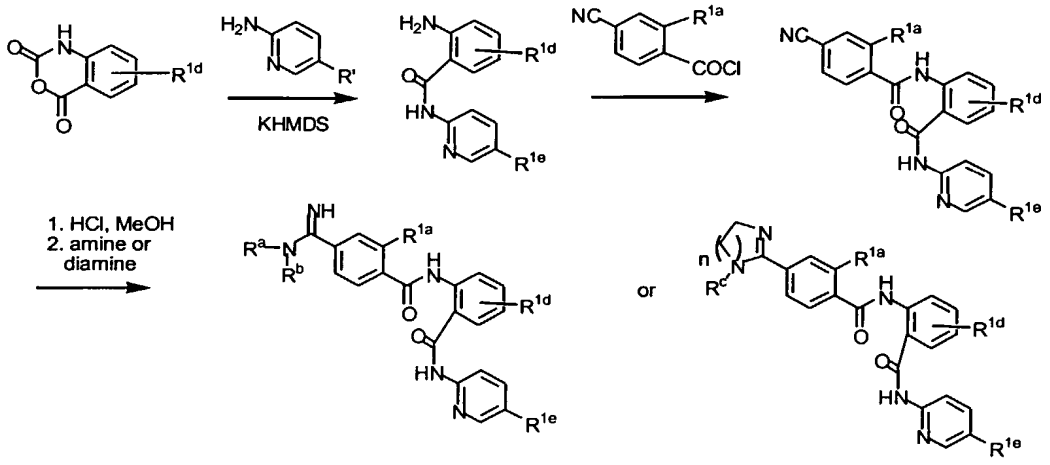
Scheme 8



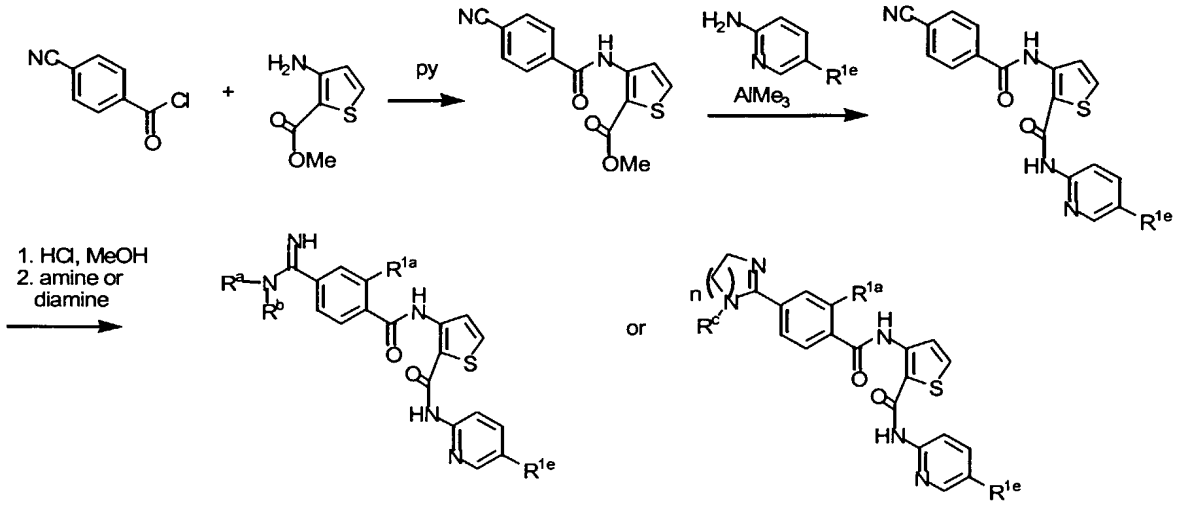
Scheme 9



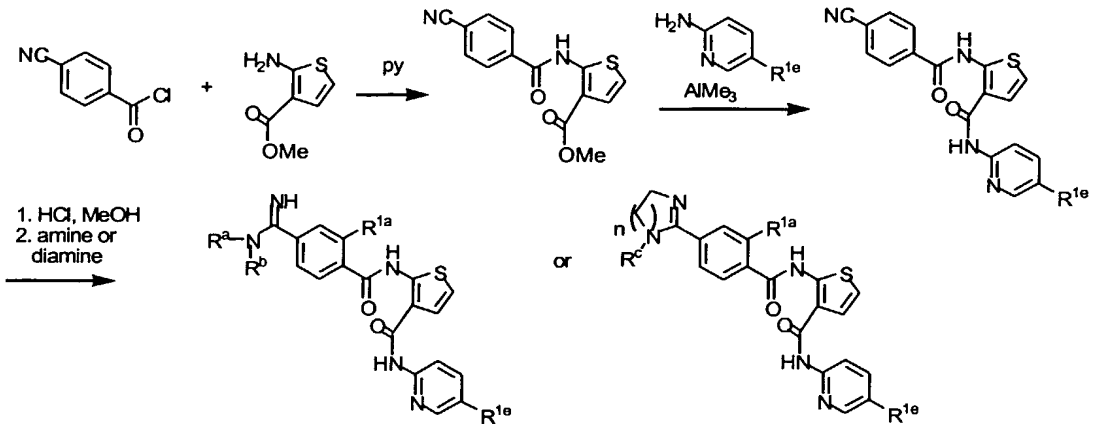
Scheme 10



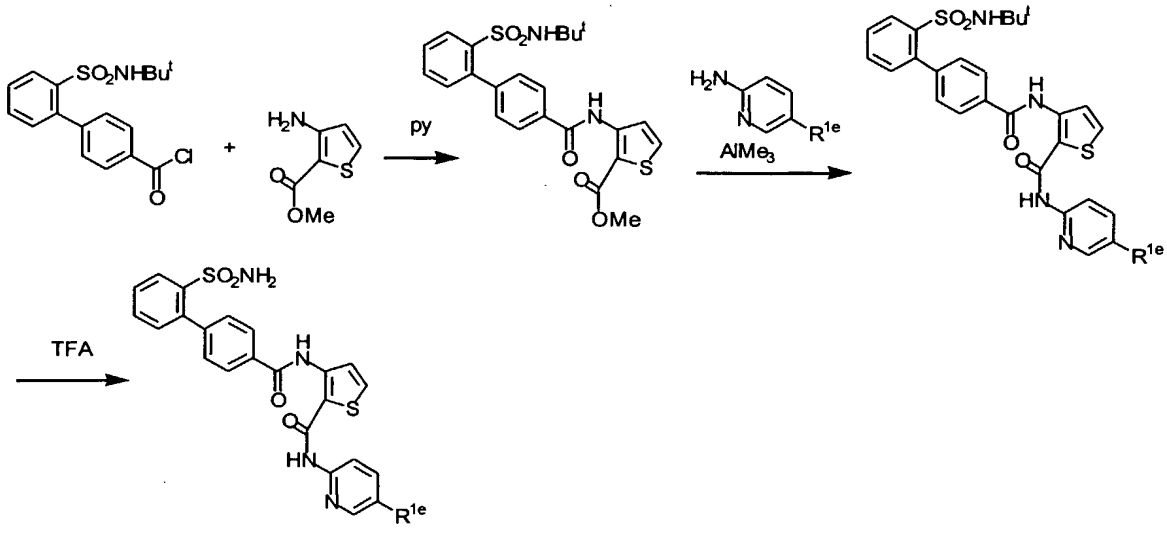
Scheme 11



Scheme 12



Scheme 13



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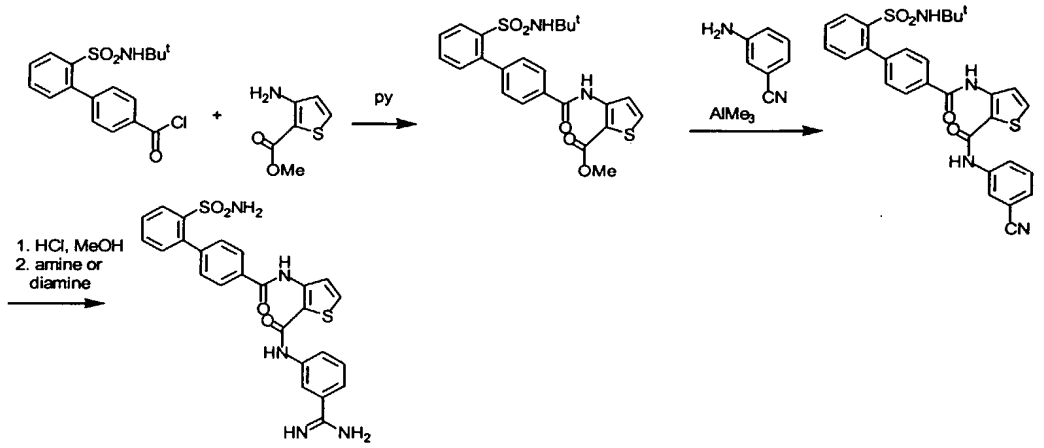
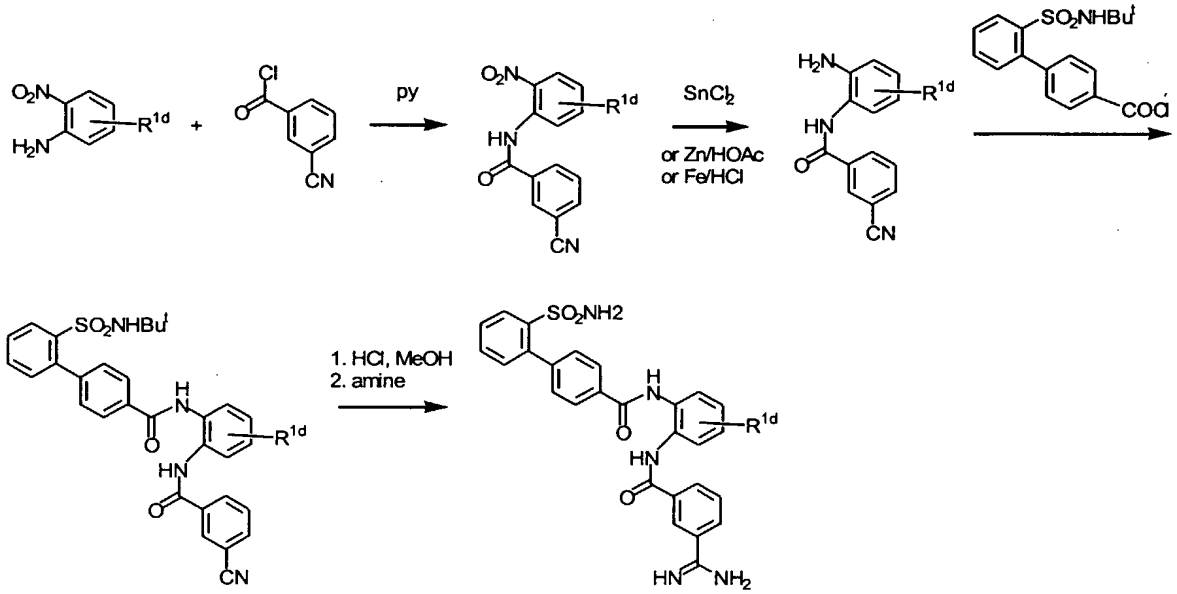
Scheme 14



Scheme 15



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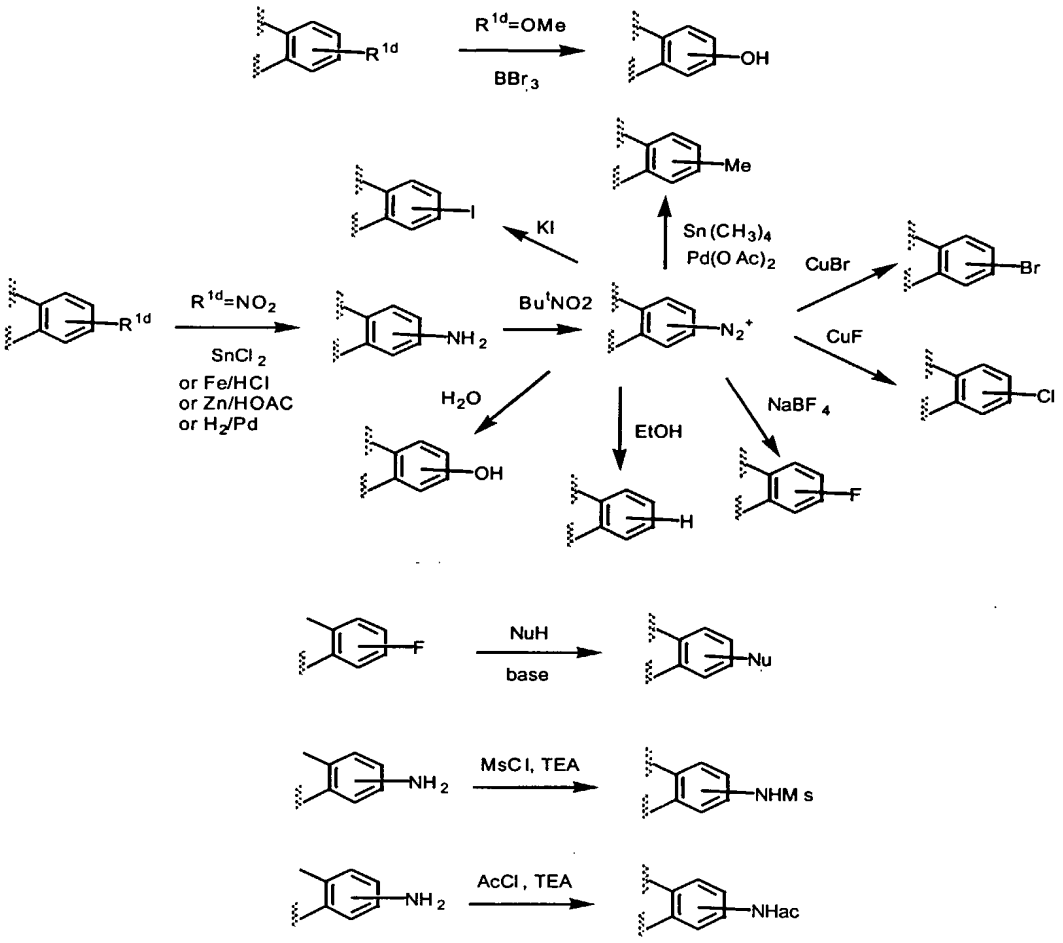
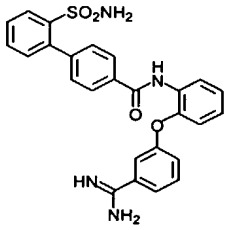
Scheme 16: Transformations of R^{1d}



Example 1

3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine.



Step 1: To a solution of 2-fluoro nitrobenzene (1.41 g, 10 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (1.19 g, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (2.76 g, 2 equiv). After stirring at 60°C for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-nitrophenoxy)benzonitrile (2.38 g, 99%). MS found for $C_{13}H_9N_2O_3$ $(M+H)^+$: 241.

Step 2: A solution of 3-(2-nitrophenoxy)benzonitrile (1.21 g, 5 mmol, 1.0 equiv) in 30 mL of EtOH was treated with $SnCl_2 2H_2O$ (3.38 g, 3 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to give 3-(2-aminophenoxy)benzonitrile (1.04 g, 99%). MS found for $C_{13}H_{11}N_2O$ $(M+H)^+$: 211.

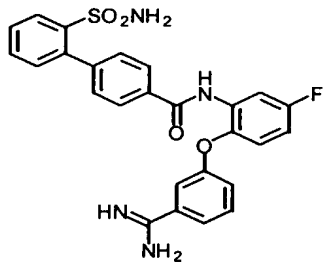
Step 3: A mixture of 3-(2-aminophenoxy)benzonitrile (210 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (300 mg, 57%). MS found for $C_{30}H_{28}N_3O_4S$ $(M+H)^+$: 526.

Step 4: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5

equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino) phenoxy)benzamidine (40 mg, 83%). MS found for $C_{26}H_{23}N_4O_4S$ $(M+H)^+$: 487.

Example 2

3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

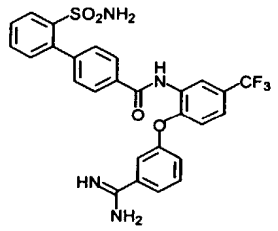


Step 1: A mixture of 3-(2-amino-4-fluorophenoxy)benzonitrile (230mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (495 mg, 91%). MS found for $C_{30}H_{27}FN_3O_4S$ $(M+H)^+$: 544.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-fluoro-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (55 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-fluoro-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (39 mg, 77%). MS found for $C_{26}H_{22}FN_4O_4S$ $(M+H)^+$: 505.

Example 3

3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

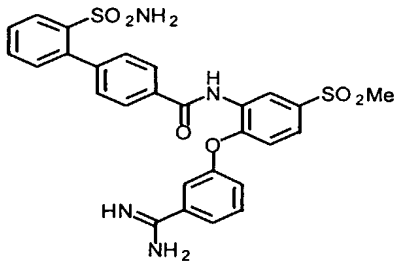


Step 1: A mixture of 3-(2-amino-4-trifluoromethylphenoxy)benzonitrile (280 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (529 mg, 89%). MS found for $C_{31}H_{27}F_3N_3O_4S$ $(M+H)^+$: 594.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-trifluoromethyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (59 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-trifluoromethyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (35 mg, 63%). MS found for $C_{27}H_{22}F_3N_4O_4S$ $(M+H)^+$: 555.

Example 4

3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

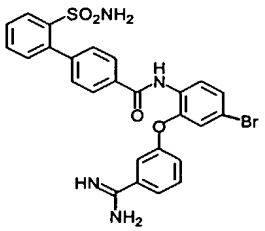


Step 1: A mixture of 3-(2-amino-4-methylsulfonylphenoxy)benzonitrile (290 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (429 mg, 71%). MS found for $C_{31}H_{30}N_3O_6S_2$ $(M+H)^+$: 604.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of 3-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (60 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (27 mg, 47%). MS found for $C_{27}H_{25}N_4O_6S_2$ $(M+H)^+$: 565.

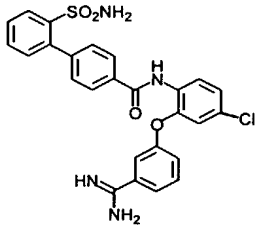
Examples 5-8

The following compounds of Examples 5-8 were prepared using the procedure described in Example 1:



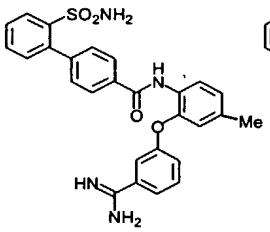
Example 5

MS (M+H): 565



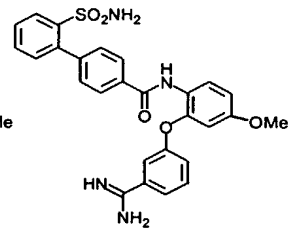
Example 6

MS (M+H): 521



Example 7

MS (M+H): 501

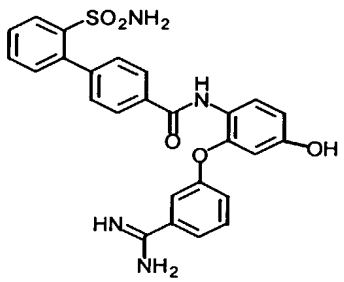


Example 8

MS (M+H): 517

Example 9

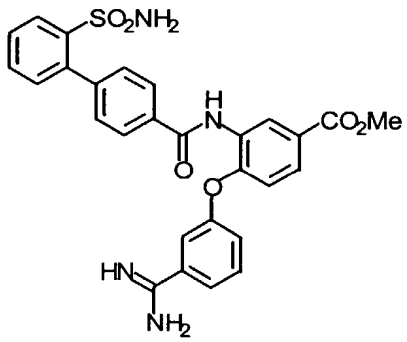
3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.



Step 1: A solution of 3-(5-methoxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino) phenoxy) benzamidine (52 mg, 0.1 mmol, 1 equiv) in 5 mL of methylene chloride was treated with BBr_3 (1 M in dichloromethane, 0.5 mL, 5 equiv) overnight. The reaction was quenched with water carefully and after the volatile was evaporated, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(5-hydroxy-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine. (41 mg, 82%). MS found for $C_{26}H_{23}N_4O_6S$ $(M+H)^+$: 503.

Example 10

3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

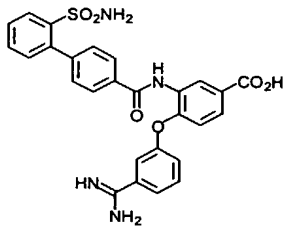


Step 1: A mixture of 3-(2-amino-4-methoxycarbonylphenoxy)benzonitrile (270 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (502 mg, 86%). MS found for $C_{32}H_{30}N_3O_6S$ $(M+H)^+$: 584.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(4-methoxycarbonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzonitrile (58 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (29.5 mg, 54%). MS found for $C_{28}H_{25}N_4O_6S$ $(M+H)^+$: 545.

Example 11

3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine.

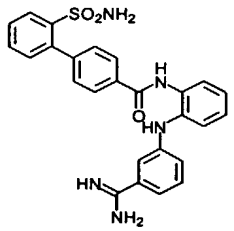


A solution of 3-(4-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (10.9 mg, 0.02 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h.

Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-(4-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) benzamidine (8.9 mg, 84%). MS found for $C_{27}H_{23}N_4O_6S$ $(M+H)^+$: 531.

Example 12

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine.

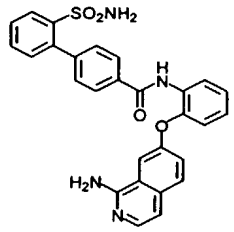


Step 1: A mixture of 3-(2-amino-phenylamino)benzonitrile (196 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino) phenylamino) benzonitrile (226 mg, 43%). MS found for $C_{30}H_{29}N_4O_3S$ $(M+H)^+$: 525.

Step 2: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzonitrile (53 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pheylamino) benzamidine (27 mg, 55%). MS found for $C_{26}H_{24}N_5O_3S$ $(M+H)^+$: 486.

Example 13

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline.



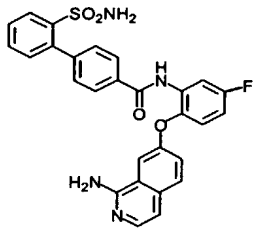
Step 1: A mixture of 7-(2-aminophenoxy)isoquinoline (237 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (469 mg, 85%). MS found for $C_{32}H_{30}N_3O_4S$ $(M+H)^+$: 552.

Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy) isoquinoline (110 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 2 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyridine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)phenoxy)-1-aminoisoquinoline (43 mg, 42%). MS found for $C_{28}H_{23}N_4O_4S$ $(M+H)^+$: 511.

Example 14

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy)1-aminoisoquinoline.



Step 1: A mixture of 7-(2-amino-4-fluorophenoxy)isoquinoline (255 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (467 mg, 82%). MS found for $C_{32}H_{29}FN_3O_4S$ $(M+H)^+$: 570.

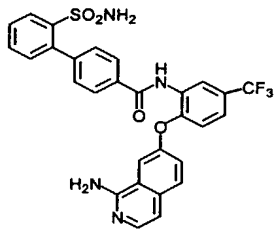
Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-fluorophenoxy) isoquinoline (114, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-

4-fluorophenoxy)1-aminoisoquinoline (77 mg, 50%). MS found for $C_{28}H_{22}FN_4O_4S$ $(M+H)^+$: 529.

Example 15

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline.



Step 1: A mixture of 7-(2-amino-4-trifluoromethylphenoxy)isoquinoline (305 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (360 mg, 58%). MS found for $C_{33}H_{29}F_3N_3O_4S$ $(M+H)^+$: 620.

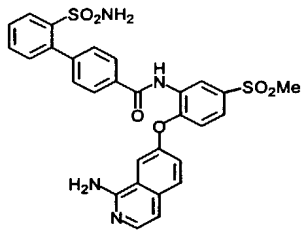
Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy) isoquinoline (124 mg, 0.2 mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried ove $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After

removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-trifluoromethylphenoxy)1-aminoisoquinoline (64 mg, 52%). MS found for $C_{29}H_{22}F_3N_4O_4S$ $(M+H)^+$: 579.

Example 16

7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline.



Step 1: A mixture of 7-(2-amino-4-methylsulfonylphenoxy)isoquinoline (315 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1 equiv), Bop reagent (880 mg, 2 equiv) and TEA (1.39 mL, 10 equiv) in 3 mL of DMF was stirred at rt overnight. The mixture was diluted with EtOAc, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (460 mg, 73%). MS found for $C_{33}H_{32}N_3O_6S_2$ $(M+H)^+$: 630.

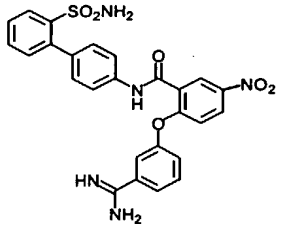
Step 2: A solution of 7-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)-4-methlsulfonylphenoxy) isoquinoline (126 mg, 0.2mmol, 1 equiv) in 5 mL of acetone was treated with *m*CPBA (113 mg, 57%, 1.5 equiv) until HPLC showed complete reaction. Acetone was evaporated, the residue was partetioned between methylene chloride and saturated aqueous $NaHCO_3$. The organic layer was dried ove $MgSO_4$ and used in the next step directly.

Step 3: The compound obtained in step 4 in 5 mL of pyridine was treated with tosyl chloride (46 mg, 1.2 equiv) at rt overnight and pyrine was removed under reduced

pressure. The residue was reacted with 5 mL of ethanolamine for 12 h, and partitioned between methylene chloride and water. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 3 mL of trifluoroacetic acid for 30 min. After removing TFA, the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to give 7-(2-(4-[(2-aminosulfonyl)phenyl]benzoylamino)-4-methylsulfonylphenoxy)1-aminoisoquinoline (94 mg, 80%). MS found for $C_{29}H_{25}N_4O_6S_2$ $(M+H)^+$: 589.

Example 17

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine.



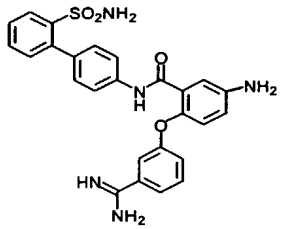
Step 1: A solution of 2-fluoro-5-nitrobenzoic acid (1.85 g, 10 mmol, 1.33 equiv) in thionyl chloride (5 mL) was refluxed for 2 h and evaporated. The residue was redissolved in 20 mL of methylene chloride and to the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]aniline (2.0 g, 1.0 equiv) and 5 mL of pyridine. After stirring at rt overnight, the volatile was evaporated. Flash chromatography on silica gel 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (2.9 g, 99%). MS found for $C_{23}H_{23}FN_3O_5S$ $(M+H)^+$: 472.

Step 2: To a solution of 1-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl)-2-fluoro-5-nitrobenzene (1.18 g, 0.25 mmol, 1.0 equiv) and 3-hydroxybenzonitrile (298 mg, 1.0 equiv) in 10 mL of DMF was added K_2CO_3 (691 mg, 2 equiv). After stirring at 60^0C for 3 h, the mixture was diluted with EtOAc and washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and chromatographied to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile(950 g, 63%). MS found for $C_{30}H_{27}N_4O_6S$ $(M+H)^+$: 571.

Step 3: A stream of HCl(g) was bubbled through a 0°C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (57 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (39 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (24 mg, 45%). MS found for $C_{26}H_{22}N_5O_6S$ $(M+H)^+$: 532.

Example 18

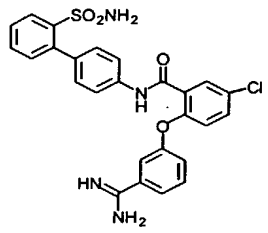
3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine.



A mixure of 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzamidine (53 mg, 0.1 mmol, 1 equiv), 5 mL of 1N HCl, 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H_2 atomosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, the aqueous residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzamidine (31 mg, 66%). MS found for $C_{26}H_{24}N_5O_4S$ $(M+H)^+$: 502.

Example 19

3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine.



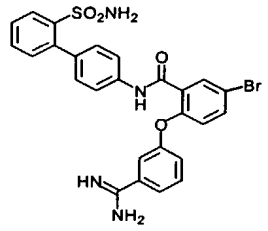
Step 1: A mixure of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-nitrophenoxy) benzonitrile (570 mg, 1 mmol, 1 equiv) and $SnCl_2.2H_2O$ (677 mg, 3 equiv) in 25 mL of EtOAc was refluxed for 2 h. The reaction was quenched with sat. $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$, filtered and evaporated to give 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (45 mg, 83%). MS found for $C_{30}H_{29}N_4O_4S$ $(M+H)^+$: 541.

Step 2: A mixure of t-$BuNO_2$ (21 mg, 0.1 mmol, 2 equiv), CuCl (20 mg, 2 equiv) in 5 mL of acetonitrile was refluxed for 10 min. To the solution was added 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-aminophenoxy) benzonitrile (54 mg, 0.1 mmol, 1 equiv). The mixture was refluxed for 1h and evaporated. Flash chromatography with 1:2 EtOAc/hexane to give [(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (43 mg, 77%)MS found for $C_{30}H_{27}ClN_3O_4S$ $(M+H)^+$: 561.

Step 3: A stream of HCl(g) was bubbled through a 0^0C solution of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzonitrile (56 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The resulting residue was treated with ammonium acetate (40 mg, 5 equiv) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN to 3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-chlorophenoxy) benzamidine (47 mg, 84%). MS found for $C_{26}H_{22}ClN_4O_4S$ $(M+H)^+$: 521.

Example 20

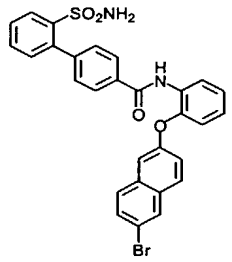
3-(2-(4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl-4-bromophenoxy) benzamidine.



This compound is prepared according to the procedure described in example 19. MS found for $C_{26}H_{22}BrN_4O_4S$ $(M+H)^+$: 565.

Example 21

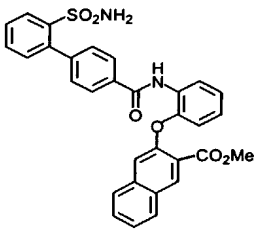
2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



A mixture of 2-bromo-6-(2-aminophenoxy) naphthalene (314 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 2-bromo-6-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (378 mg, 66%). MS found for $C_{29}H_{22}BrN_2O_4S$ $(M+H)^+$: 573.

Example 22

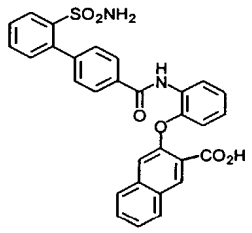
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.



A mixture of 3-methoxycarbonyl-2-(2-aminophenoxy) (294 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (420 mg, 76%). MS found for $C_{31}H_{25}N_2O_6S$ $(M+H)^+$: 553.

Example 23

3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

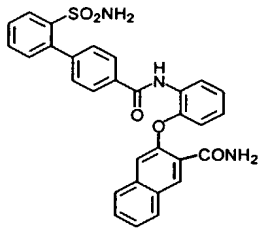


A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (55 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h.

Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (47 mg, 88%). MS found for $C_{30}H_{23}N_2O_6S$ $(M+H)^+$: 539.

Example 24

3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene.

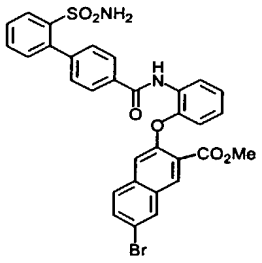


Step 1: A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (40 mg, 0.066 mmol) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, and acidified with 1N HCl until PH ~ 1-2. The product (39 mg, 100%), 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene, was extracted with EtOAc, dried over $MgSO_4$, filtered and evaporated. MS found for $C_{34}H_{31}N_2O_6S$ $(M+H)^+$: 595.

Step 2: A solution of 3-hydroxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonylamino)phenoxy) naphthalene (39 mg, 0.066 mmol) was refluxed in 3 mL of thionyl chloride for 2 h and evaporated. The residue was then stirred in 5 mL of 2M ammonia in methanol overnight. The volatile was evaporated and the residue was refluxed in 2 mL of trifluoroacetic acid overnight to give the product 3-aminocarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy naphthalene (14 mg, 39%) after HPLC (C18 reversed phase, eluting with 0.5% TFA in H_2O/CH_3CN). MS found for $C_{30}H_{24}N_3O_5S$ $(M+H)^+$: 538.

Example 25

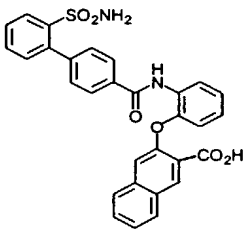
3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A mixture of 2-(2-aminophenoxy)-3-methoxycarbonyl-6-bromo naphthalene (372 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave 3-methoxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (423 mg, 67%). MS found for $C_{31}H_{24}BrN_2O6S$ $(M+H)^+$: 631.

Example 26

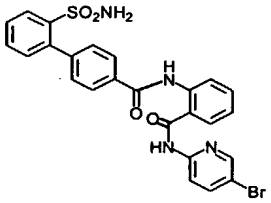
3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene.



A solution of 3-methoxycarbonyl-2-(4-methylsulfonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy)-6-bromo naphthalene (63 mg, 0.1 mmol, 1.0 equiv) in 5 mL of methanol was treated with 1N LiOH (2 mL) at rt for 2 h. Methanol was evaporated, the aqueous residue was subjected to HPLC with 0.5% TFA in H_2O/CH_3CN to give 3-hydroxycarbonyl-2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenoxy-6-bromo naphthalene (47 mg, 78%). MS found for $C_{30}H_{22}BrN_2O6S$ $(M+H)^+$: 617.

Example 27

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



Step 1: A solution of 2-ntrobenzoyl chloride (3.70 g, 20 mmol, 1.0 equiv), 2-amino-5-bromopyridine (3.50 g, 1.0 equiv), pyridine (10 mL) in 25 mL of methylene chloride was stirred overnight. The volatile was evaporated, flash chromatography on silica gel gave N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (5.02 g, 77%). MS found for $C_{12}H_9BrN_3O_3$ $(M+H)^+$: 322.

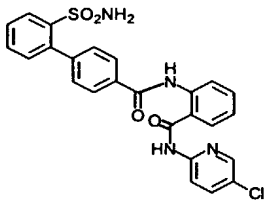
Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)phenylcarboxamide (1.0 g, 3.1 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with $SnCl_2 2H_2O$ (2.80 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ and 1N NaOH. The organic layer was dried over $MgSO_4$, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (0.89 g, 98%). MS found for $C_{12}H_{11}BrN_3O$ $(M+H)^+$: 292.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight,

washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (470 mg, 85%). MS found for $C_{25}H_{20}BrN_4O_4S$ $(M+H)^+$: 551.

Example 28

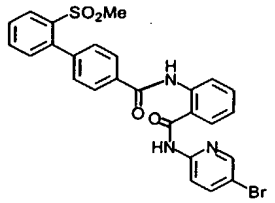
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide.



A mixture of N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (247 mg, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (349 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)phenylcarboxamide (370 mg, 73%). MS found for $C_{25}H_{20}ClN_4O_4S$ $(M+H)^+$: 507.

Example 29

N-(5-bromo-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



Step 1: To a mixture of 2-bromothioanisole (4.8g, 23.6mmol), 4-carboxybenzeneboronic acid (3.92g, 23.6mmol) and 2M K_2CO_3 (35.5mmol, 71mmol) in dioxane (20ml) was added dichlorobis(triphenylphosphine)palladium (II) (415mg, 0.6mmol) under Ar. It was refluxed for 2hrs. After the removal of the solvent, the residue was neutralized by 1N HCl and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 4-[(2-methylthio)phenyl]benzoic acid (5.9g, 100%). ES-MS $(M+H)^+$=245.

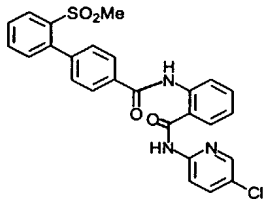
Step 2: To a solution of 4-[(2-methylthio)phenyl]benzoic acid (3.43g, 14mmol) in H_2O (10ml) and acetone (20ml) was added oxone monopersulfate (34.6g, 56mmol). The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 2.16g (63%) 4-[(2-methylsulfonyl)phenyl]benzoic acid. ES-MS $(M+H)^+$=277.

Step 3: To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (552mg, 2mmol) in dichloromethane (5ml) was added oxalyl chloride (350ul, 4mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (700mg, 2.4mmol), pyridine (486ul, 6mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 414mg (38%) of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-

methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M^+=550, $(M+2)^+$=552.

Example 30

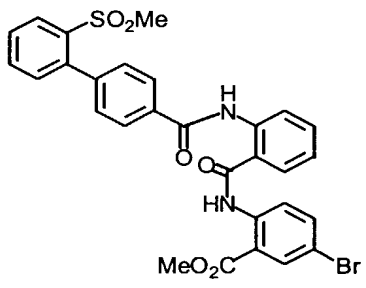
N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



To a solution of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol) in dichloromethane (5ml) was added oxalyl chloride (175 ul, 2 mmol) and 2 drops of DMF. The mixture was stirred at r.t. for 2 hrs. After the removal of the solvent *in vacuo*, the residue was dissolved in dichloromethane (5ml), N-(5-chloro-2-pyridinyl)-(2-amino)phenylcarboxamide (297mg, 1.2 mmol), pyridine (243ul, 3 mmol) and catalytic amount of DMAP were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column (30% ethyl acetate/hexane) and then preparative HPLC to get 95 mg (20%) of N-(5-chloro-2-pyridinyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. ES-MS M+=505.5, (M+2)+=507.5.

Example 31

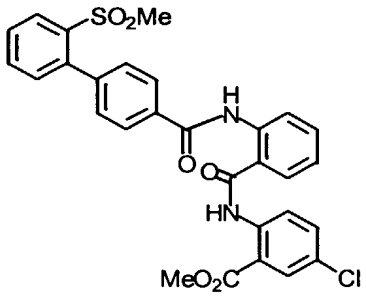
N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-bromo-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (348 mg,1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 480 mg (79%) of N-(4-bromo-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}BrN_2O_6S$ $(M+H)^+$: 607.

Example 32

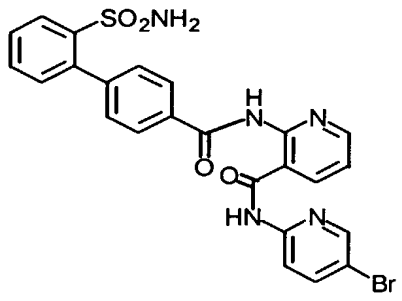
N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



A sample of 4-[(2-methylsulfonyl)phenyl]benzoic acid (280 mg, 1 mmol, 1 equiv) was refluxed with 2 mL of thionyl chloride for 2 h and evaporated. The residue was dissolved in 5 mL of dichloromethane, N-(4-chloro-2-methoxycarbonyphenyl)-(2-amino)phenylcarboxamide (304 mg,1 equiv), pyridine (3 mL) were added. The mixture was stirred at r.t. overnight. After the removal of the solvent, the residue was purified by flash column to give 479 mg (85%) of N-(4-chloro-2-methoxycarbonyphenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide. MS found for $C_{29}H_{24}ClN_2O_6S$ $(M+H)^+$: 563.

Example 33

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.

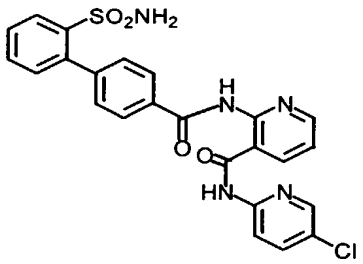


Step 1: A solution of 2-aminopyridine-3-carboxylic acid (138 mg, 1 mmol) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid and $POCl_3$. The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered and flash chromatographied to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (243 mg, 52%). MS found for $C_{24}H_{26}N_3O_5S$ $(M+H)^+$: 468.

Step 2: To A solution of 2-amino-5-bromopridine (45 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (17 mg, 48%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 34

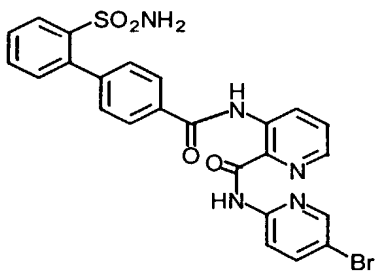
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



To A solution of 2-amino-5-chloropridine (32 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.65 mL, 20 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-3-carboxylate (30 mg, 0.064 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (21 mg, 66%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

Example 35

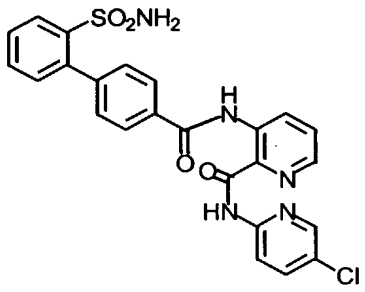
N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide.



To A solution of 2-amino-5-bromopridine (69.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-bromo-2-pyridinyl)-(3-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-2-carboxamide (29 mg, 53%). MS found for $C_{24}H_{19}BrN_5O_4S$ $(M+H)^+$: 552.

Example 36

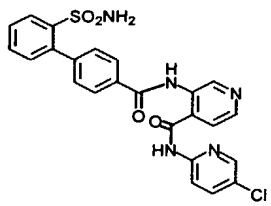
N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide.



To A solution of 2-amino-5-chloropridine (51.2 mg, 4.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 1 mL, 20 equiv) for 30 min was added 3-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)aminopyridine-2-carboxylate (46.7 mg, 0.1mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in H_2O/CH_3CN gave N-(5-chloro-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)pyridinyl-3-carboxamide (33 mg, 64%). MS found for $C_{24}H_{19}ClN_5O_4S$ $(M+H)^+$: 508.

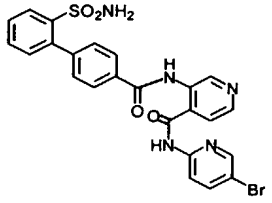
Examples 37-40

The following compounds of Examples 37-40 were prepared using the procedure described in Example 36:



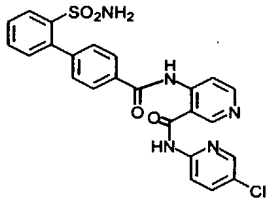
Example 37

MS (M+H): 508



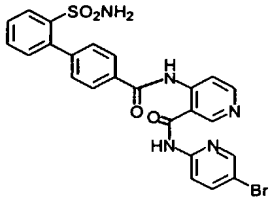
Example 38

MS (M+H): 552



Example 39

MS (M+H): 508

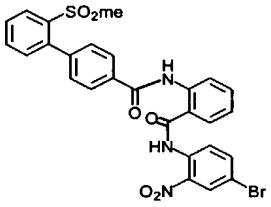


Example 40

MS (M+H): 552

Example 41

N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide.



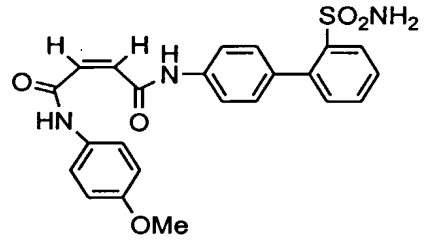
Step 1: A mixture of methyl 2-aminobenzoate (150 mg, 1 mmol, 1.0 equiv), 4-[(2-methylsulfonyl)phenyl]benzoic chloride (294 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H_2O. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (250 mg, 54%). MS found for $C_{25}H_{27}N_2O_5S$ $(M+H)^+$: 467.

Step 2: To a solution of 4-bromo-2-ntroaniline (43.4 mg, 0.2 mmol, 2.0 equiv) in 5 mL of methylene chloride treated with $AlMe_3$ (2M in hexane, 0.3 mL, 6 equiv) for 30

min was added methyl 2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)aminobenzoate (46.6 mg, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over $MgSO_4$, filtered and evaporated. Flash chromatography on silica gel gave N-(4-bromo-2-nitrophenyl)-(2-(4-[(2-methylsulfonyl)phenyl]phenylcarbonyl)amino)phenylcarboxamide (5 mg, 9%). MS found for $C_{27}H_{21}BrN_3O_6S$ $(M+H)^+$: 594.

Example 42

N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide



A. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide.

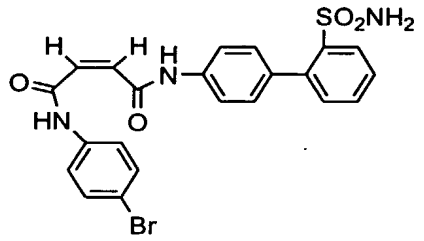
To a solution of commercially available N-(4-methoxyphenyl)maleamic acid (100 mg, 0.452 mmol), triethylamine (0.126 mL, 0.906 mmol) and 4-(2-tert-butylaminosulfonylphenyl)aniline (138 mg, 0.454 mmol) in anhydrous DMF (5 mL), BOP (260 mg, 0.588 mmol) was added. The mixture was stirred at room temperature overnight. Water and EtOAc were added. The organic phase was separated, washed with H2O, then with 5% NaHCO3, dried over Na2SO4, concentrated in vacuo. The residue was purified by HPLC using a gradient of 20% CH3CN in H2O (containing 0.1% TFA) to 100% CH3CN over 80 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (70 mg, yield: 31%). MS 508 (M + H).

B. Preparation of N-(4-methoxyphenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

The compound N-(4-methoxyphenyl)-N'-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)-maleamic amide (40 mg, 79 mol) was dissolved in TFA (3 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH3CN in H2O (containing 0.1% TFA) to 95% CH3CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (18 mg, yield: 51%). MS 452 (M + H) and 474 (M + Na). ^{1}H NMR (CDCl3) 11.40 (br.s, 1H), 10.28 (br.s, 1H), 8.12 (d, 1H, J = 8 Hz), 7.72 (d, 2H, J = 8 Hz), 7.60 – 7.20 (m, 9H), 6.86 (AB type, 2H), 6.45 (br.s, 2H), 3.79 (s, 3H).

Example 43

N-(4-bromophenyl)-N'-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.



A. Preparation of N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester.

To a solution of commercially available maleic acid monomethyl ester (277 mg, 2.13 mmol), 4-(2-tert-butylaminosulfonylphenyl)aniline (648 mg, 2.13 mmol) and triethylamine (0.593 mL, 4.26 mmol) in CH2Cl2 (20 mL), BOP (1.13 g, 2.55 mmol) was added. The mixture was stirred at room temperature overnight. More maleic acid monomethyl ester (50 mg, 0.385 mmol) was added. It was stirred for 3 hours. The CH2Cl2 solution was then washed with sat. NaHCO3, 1N HCl and sat. NaCl. The solution was dried over Na2SO4, concentrated in vacuo. The residue was purified by a silica gel column using a gradient of 10-40% EtOAc in hexane as solvents, to give the titled compound (360 mg, yield: 41%). MS 361 (M + H - ^{t}Bu) and 439 (M + Na).